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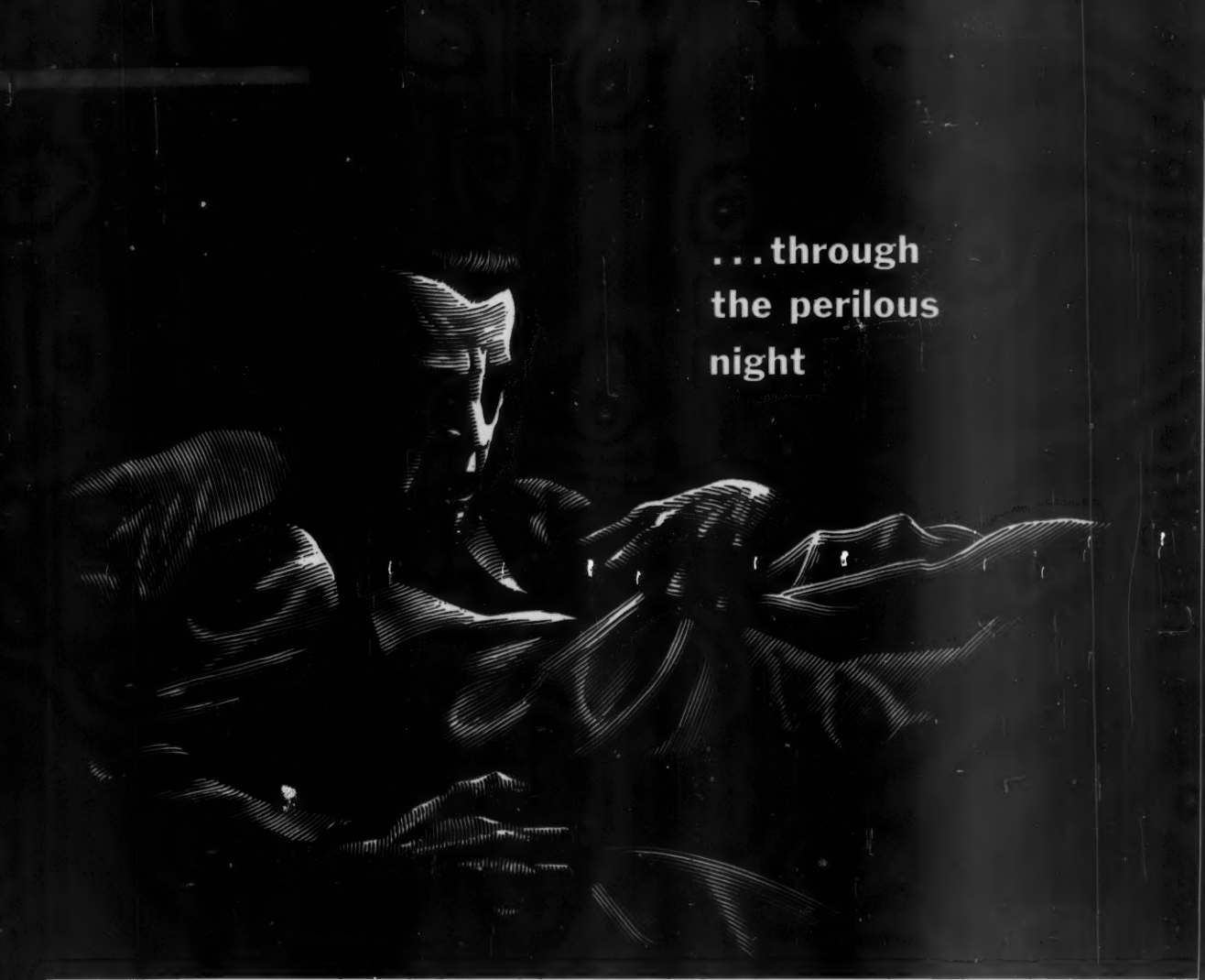

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1. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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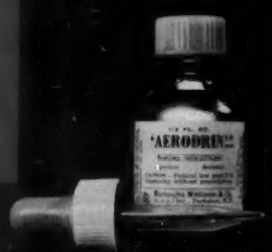

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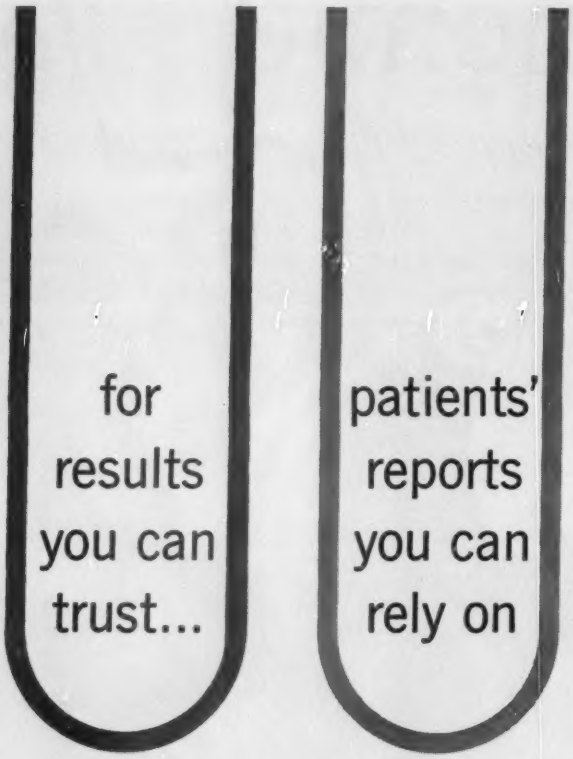
References: 1. J.A.M.A. 149:1188, 1952. 2. Ann. Int. Med. 42:9, 1955. 3. Gout and Gouty Arthritis, Modern Medical Monograph, 7, New York, Grune & Stratton, 1953, p. 80.



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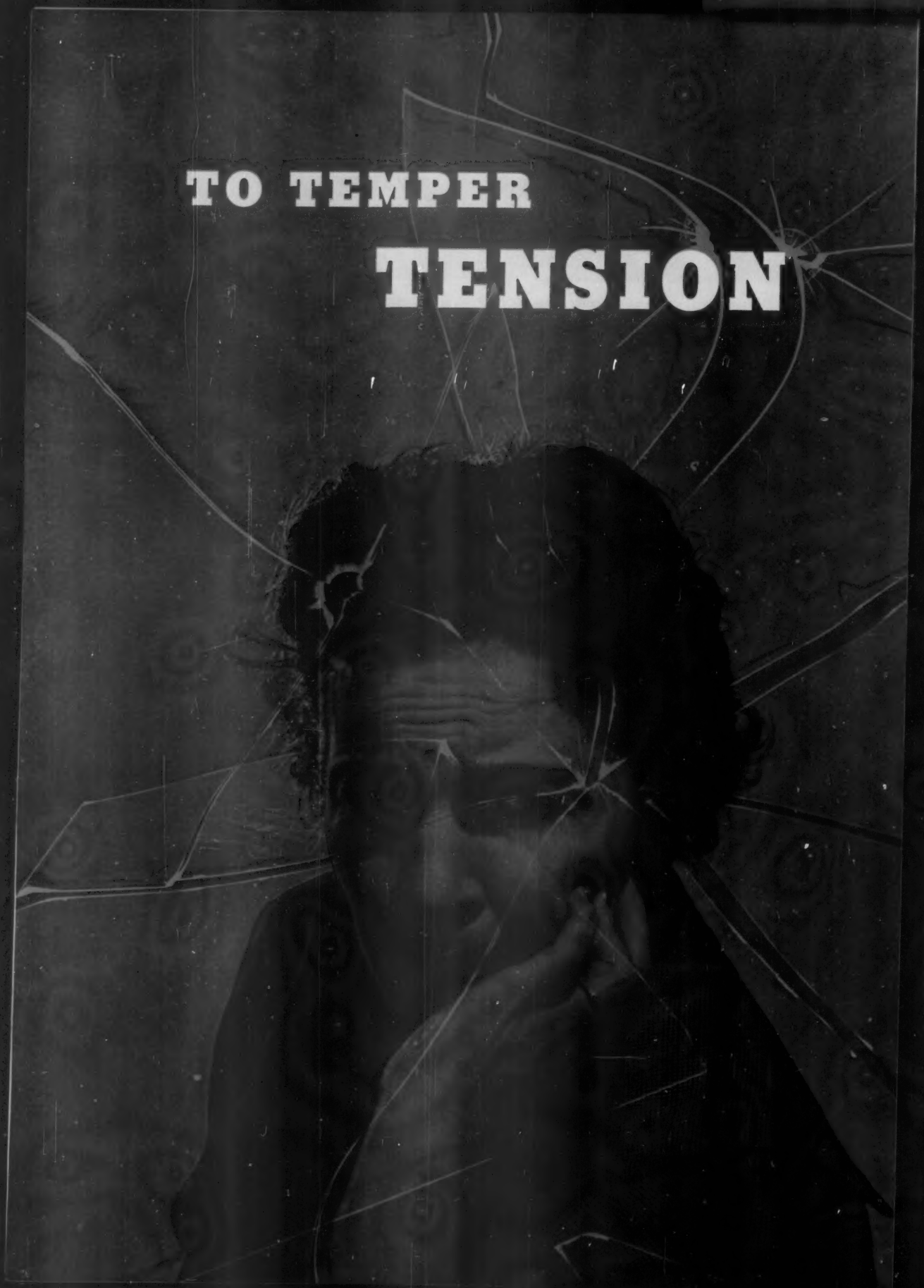
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1. Butler T. C.; Mahaffee, C., and Waddell, W. J.: Phenobarbital: Studies of Elimination, Accumulation, Tolerance, and Dosage Schedules, J. Pharmacol. & Exper. Therap. 111:425 (Aug.) 1954.

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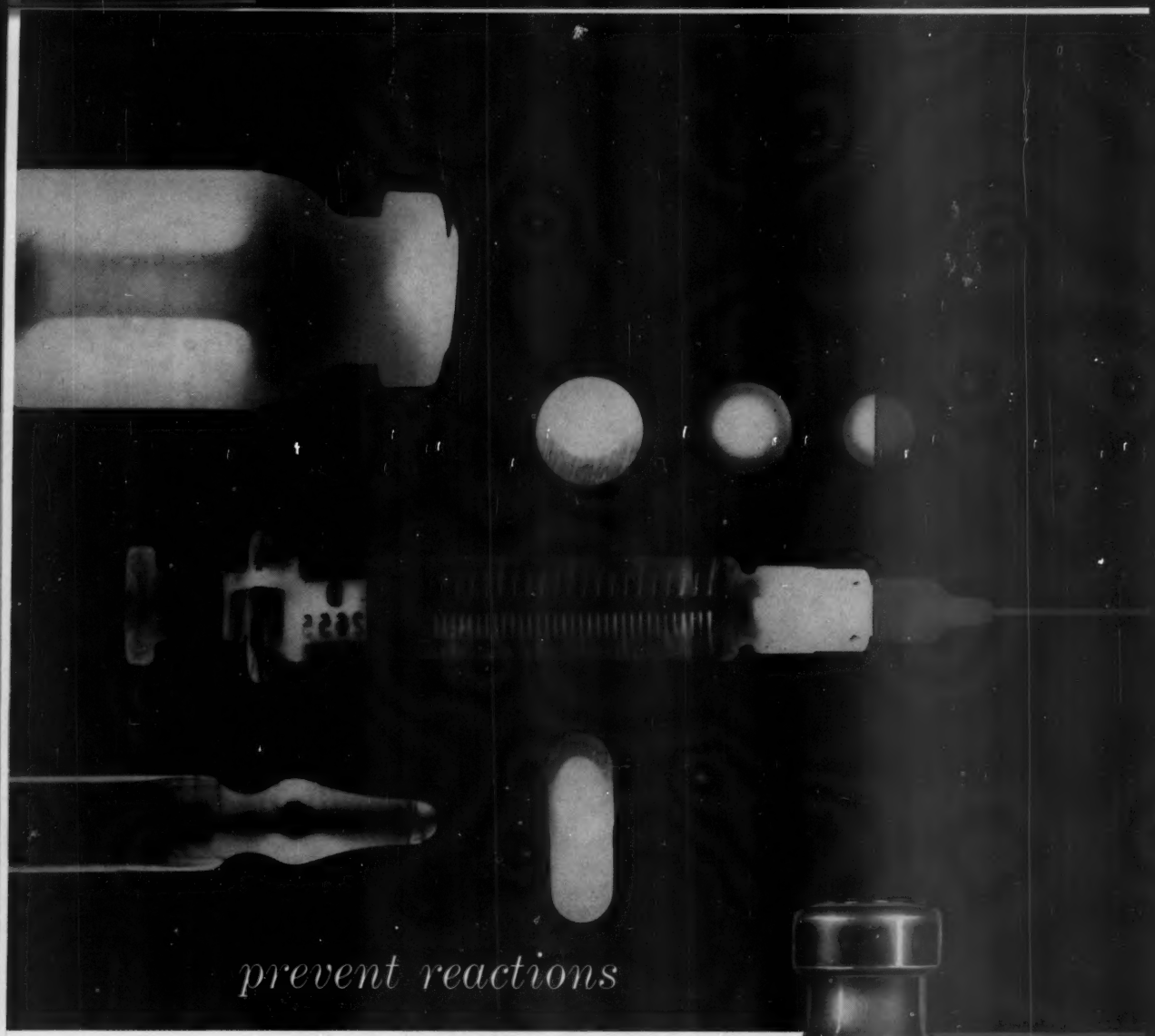

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Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
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Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4-6 hours until toxic or therapeutic effect appears (usually 24-48 hours.)
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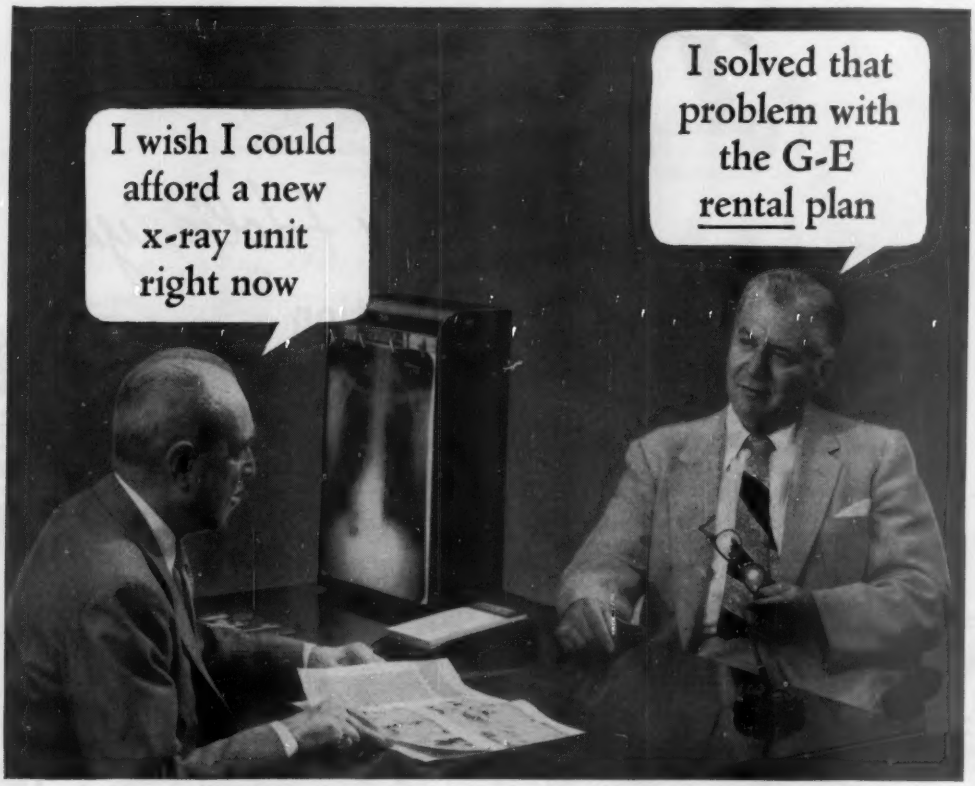

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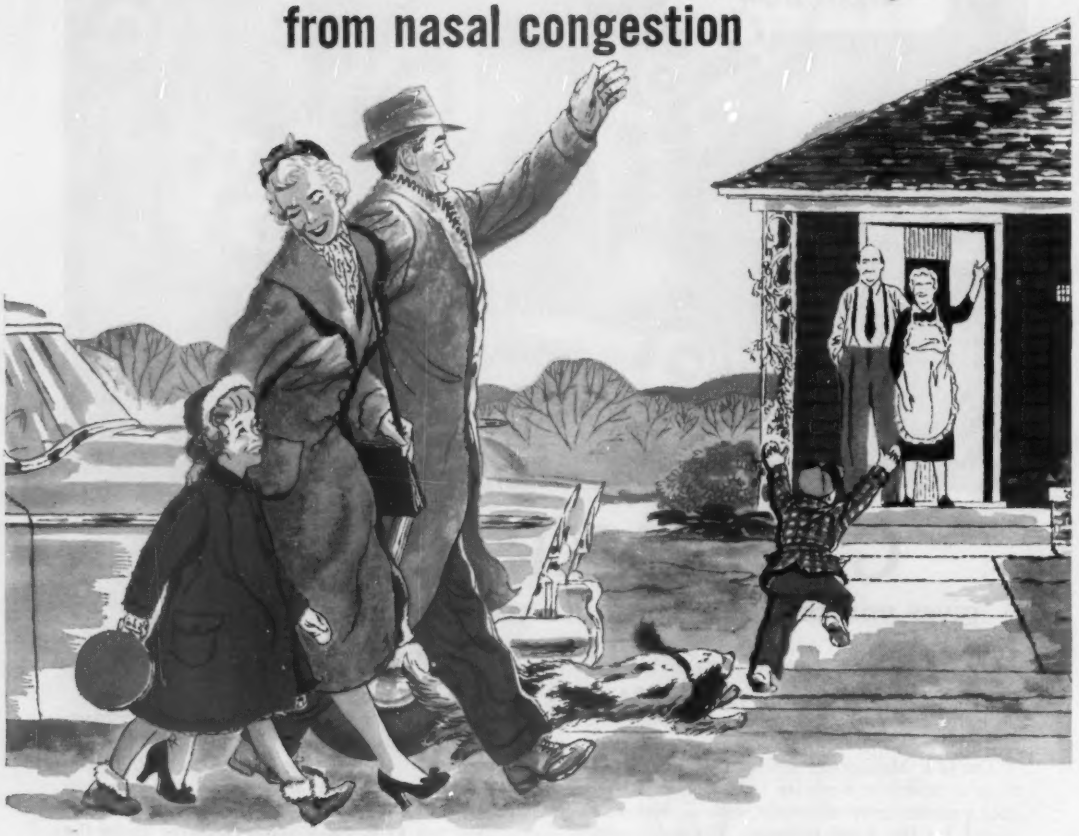

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The New England
Journal of Medicine

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Volume 253 NOVEMBER 17, 1955 Number 20

INCIDENCE OF POLIOMYELITIS IN PREGNANCY*

Its Relation to Maternal Age, Parity and Gestational Period

MORRIS SIEGEL, M.D.,† AND MORRIS GREENBERG, M.D.‡

NEW YORK CITY

PREGNANCY has long been considered one of the host factors disposing to the occurrence of poliomyelitis. An increase in susceptibility has been observed in animal studies, clinical case reports and surveys of both hospitalized cases and population groups.[1-17] Currently, however, the validity of an association between pregnancy and poliomyelitis has been questioned as a result of recent investigations of population groups in which no significant increase in incidence and mortality could be demonstrated.[5,13] Because of the conflicting evidence and the need for additional data on a community-wide basis, the susceptibility of the host during pregnancy was investigated. Three aspects of the problem were considered: the incidence and severity of clinical infection, and the effect on the fetus and newborn infant. In the present report, the plan of study and the data on incidence and clinical severity are presented.

METHOD OF STUDY

The study was based on reported cases of poliomyelitis occurring in New York City from 1949 to 1953, inclusive. The cases reported during the five-year period were seen within a week of notification by a diagnostician for the confirmation of clinical diagnosis and the collection of epidemiologic data. The diagnosis of poliomyelitis was based on the presence of three or more of the following criteria: an acute onset, with fever; stiff neck or back; increased white-cell count in the spinal fluid; increased protein in the spinal fluid; and flaccid paralysis. About 20 to 25 per cent of reported illnesses failed to meet these minimal diagnostic criteria and were excluded from the study.

Patients in the childbearing age were again visited within three or four months for additional data on paralysis, marital status and evidence of pregnancy at the time of the attack of poliomyelitis. Those who were pregnant at the onset of poliomyelitis were further followed for information on the condition of the newborn infant at the time of delivery and a year later. All the clinical and epidemiologic data were obtained by experienced diagnosticians of the Bureau of Preventable Diseases of the Department of Health.

The investigation was necessarily limited to females fifteen to forty-four years of age, a group encompassing the childbearing period responsible for 99.8 per cent of all births. The population at risk was determined from data obtained in the 1950 census, and the annual number of reported live births and fetal deaths. The incomplete reporting of fetal deaths required correction. The degree of underreporting in New York City was found to vary from 67 per cent in the first trimester to 34 per cent in the second and 14 per cent in the third.[18] Correction on this basis doubled the reported number of fetal deaths, making the adjusted figure 200 per 1000 live births.[19] The adjusted ratio was within the range of expectancy based on confidential histories of women attending birth-control clinics in New York City.[20,21]

The duration of gestation and the number of pregnancies were considered in the calculation of incidence on an annual basis. We carried this out by converting the number of live births and fetal deaths occurring each year into person years of gestation by multiplying the number reported by their respective weeks of gestation and dividing the sum by 52. These calculations were made for each of the maternal age groups. The sum of the respective totals in each age group gave the number of person years of gestation between fifteen and forty-four years of age, inclusive. These totals represent estimates of the number of women pregnant in the general population during the period of investigation, and served as the denominator in calculation of the age-specific annual incidence of poliomyelitis during pregnancy. We determined the nonpregnant female population by subtracting the foregoing totals from the female census population for 1950.

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Results

Population at Risk

A summary of the number of women pregnant during the five-year period of study is given in Table 1 by maternal age, number of pregnancies and person years of gestation. A total of 886,227 live births and fetal deaths were reported in age groups fifteen to forty-four from 1949 to 1953, inclusive. Adjustment for under-reporting of fetal deaths raised the total number of pregnancies to 964,198, or a little less than 200,000 per year. This was converted to person years of gestation as indicated above. The estimated number was 686,287, or 77.4 per cent, of the total number of pregnancies reported in five years. On an annual basis, the average number of person years of gestation was about 137,000. This figure, which represents an estimate of the average number of women pregnant at any one time, comprised about 7 per cent of the general female population fifteen to forty-four years of age. About 61 per cent of the women pregnant were twenty to twenty-nine, and 31 per cent thirty to thirty-nine years of age. The remaining 8 per cent were in the age groups fifteen to nineteen and forty to forty-four. About 0.2 per cent of all reported pregnancies occurred in persons under fifteen years of age or forty-five years and over and were excluded from the study.

TABLE 1. *Number of Parturient Women by Age, New York City, 1949-1953 Inclusive.*

AGE	LIVE BIRTHS	FETAL DEATHS		TOTALS		PERSON YEARS OF GESTATION
	REPORTED NO.	REPORTED NO.	ADJUSTED NO.	REPORTED NO.	ADJUSTED NO.	
yr.						
15-19	46,459	4,230	8,059	50,689	54,518	39,081(5.6%)
20-24	226,584	20,415	38,871	246,999	265,455	192,863(28.1%)
25-29	265,287	25,571	48,689	290,858	313,976	225,959(32.9%)
30-34	166,941	19,582	37,281	186,523	204,222	142,708(20.8%)
35-39	78,386	12,382	23,579	90,768	101,965	70,727(10.4%)
40-44	16,323	4,067	7,739	20,390	24,062	14,949(2.3%)
Totals	799,980	86,247	164,218	886,227	964,198	686,287(100.0%)

A summary of the female population of childbearing age by pregnancy status and age during the period of study is given in Table 2. The nonpregnant group showed a more even age distribution than the pregnant, with a high percentage of persons in every age period. Differences in age distribution were adjusted by use of standardized rates, age-specific rates or expected values based on rates in the general female population.

Age-Specific Incidence Rates

During the five-year period of study, a total of 643 cases of poliomyelitis were reported in females fifteen to forty-four years of age for an average annual incidence of 6.6 per 100,000. The distribution of the cases reported by pregnancy status, clinical type and age are summarized in Table 3. The annual crude incidence of poliomyelitis in pregnant women was 12.7 per 100,000 person years of gestation, in contrast to an incidence of 6.1 for nonpregnant females. The crude rates exaggerate the extent of the increase in the pregnant group because of its population distribution, as already noted. When this factor is considered, as in a comparison of observed and expected values, the increase in incidence during pregnancy is reduced considerably. Thus, the observed number of cases in pregnant women was 87 whereas the expected number was 54.8, a difference of 32.2 cases, or 58.8 per cent more than expected. This increase for all clinical types of cases was considered statistically significant.* The percentage increase in the number of cases during pregnancy was approximately the same for paralytic and nonparalytic types of poliomyelitis (Table 4).

The increase in incidence observed during pregnancy varied considerably with maternal age, as shown by the age-specific rates for pregnant and nonpregnant women given in Table 3. This result may be seen more clearly in Figure 1, which shows graphically the age-specific incidence of all clinical cases and of paralytic cases in pregnant and nonpregnant groups. The rates were consistently higher in pregnant women than in the nonpregnant. In addition, the incidence declined less sharply with age in the pregnant group. As a result, the relative difference in rates between pregnant and nonpregnant groups increased with age from fifteen to thirty-nine years. Over forty years of age, the incidence of poliomyelitis was too low and the number of pregnancies too few for comparative study.

TABLE 2. *Age Distribution of Females in Childbearing Age by Pregnancy Status, New York City, 1949-1953.*

AGE	PERSON YEARS		
	TOTALS	PREGNANT GROUP	NONPREGNANT GROUP
yr.			
15-19	1,201,000(12.4%)	39,000(5.7%)	1,162,000(12.9%)
20-24	1,599,000(16.4%)	193,000(28.1%)	1,406,000(15.5%)
25-29	1,759,000(18.0%)	226,000(32.9%)	1,533,000(17.0%)
30-34	1,710,000(17.6%)	143,000(20.8%)	1,567,000(17.3%)
35-39	1,795,000(18.5%)	71,000(10.3%)	1,724,000(19.1%)
40-44	1,664,000(17.1%)	15,000(2.2%)	1,649,000(18.2%)
Totals	9,728,000(100.0%)	687,000(100.0%)	9,041,000(100.0%)

Relation to Previous Live Births

The relative increase in incidence of poliomyelitis with maternal age, discussed above, posed the question whether age alone or some factor associated with age caused the increase. One of these factors is the number of children in the household, since this, too,

*A probability of less than 0.05 was considered significant in the present study.

varies with maternal age, and since clinical infection is usually associated with children.

A direct comparison of incidence rates for poliomyelitis in pregnant and nonpregnant women by City according to the 1950 census. For all clinical cases, the standardized rates in pregnant women with previous live births were two to four times greater than the rate observed in women without previous

TABLE 3. *Average Annual Incidence of Poliomyelitis in Females Fifteen to Forty-four Years of Age by Pregnancy Status and Age, New York City, 1949-1953.*

AGE	TOTAL AVERAGE ANNUAL RATE PER 100,000 PERSON YEARS			TOTAL AVERAGE ANNUAL RATE PER 100,000 PERSON YEARS IN PREGNANT GROUP			TOTAL AVERAGE ANNUAL RATE PER 100,000 PERSON YEARS IN NONPREGNANT GROUP		
	PERSON YEARS	CASES	RATE	PERSON YEARS	CASES	RATE	PERSON YEARS	CASES	RATE
yr.									
All clinical cases:									
15-19	1,201,000	190	15.8	39,000	7	17.9	1,162,000	183	15.7
20-24	1,599,000	154	9.6	193,000	23	11.9	1,406,000	131	9.3
25-29	1,759,000	169	9.6	226,000	38	16.8	1,533,000	131	8.5
30-34	1,710,000	79	4.6	143,000	14	9.8	1,567,000	65	4.1
35-39	1,795,000	38	2.1	71,000	5	7.1	1,724,000	33	1.9
40-44	1,664,000	13	0.8	15,000	0	0.0	1,649,000	13	0.8
Totals	9,728,000	643		687,000	87		9,041,000	556	
Averages			6.6			12.7			6.1
Paralytic cases only:									
15-19	1,201,000	133	11.1	39,000	6	15.3	1,162,000	127	10.9
20-24	1,599,000	110	6.9	193,000	13	6.7	1,406,000	97	6.9
25-29	1,759,000	126	7.2	226,000	30	13.3	1,533,000	96	6.3
30-34	1,710,000	63	3.7	143,000	11	7.7	1,567,000	52	3.3
35-39	1,795,000	25	1.4	71,000	4	5.7	1,724,000	21	1.2
40-44	1,664,000	7	0.4	15,000	0	0.0	1,649,000	7	0.4
Totals	9,728,000	464		687,000	64		9,041,000	400	
Averages			4.8			9.3			4.4

family size and age could not be made because no statistics are available for such distribution in the general population. An approach to the problem presented itself through the use of data on the number of previous live births in the total pregnant population at risk and in those in whom poliomyelitis developed during pregnancy. With these facts it was possible to compare the rates in the pregnant women with and without previous live births. These are subdivided into three groups: patients with no previous live births; those with 1; and those with 2 or more.

The results observed in pregnant women according to the number of previous live births are summarized

TABLE 4. *Distribution of Paralytic and Nonparalytic Cases.*

TYPE OF CASE	CASES OBSERVED	CASES EXPECTED	INCREASE IN CASES
Paralytic	64	40.2	23.8 (59.2%)
Nonparalytic	23	14.6	8.4 (57.5%)
Totals	87	54.8	32.2 (58.8%)

in Table 5 for paralytic and nonparalytic cases. To allow for differences in age distribution of the pregnant population grouped by previous live births, standardized rates were calculated on the basis of a standard population of married women in New York

live births. These differences were somewhat more marked for paralytic cases than for nonparalytic cases. The differences were consistent for all ages combined and for each age group considered separately. Thus,

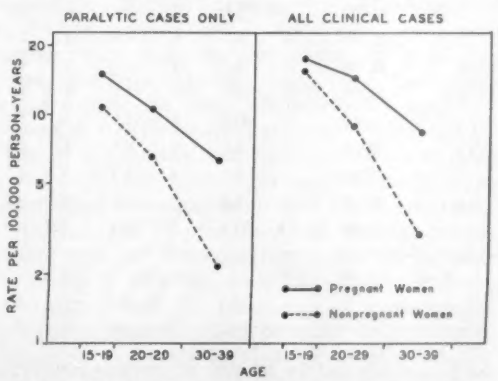

FIGURE 1. *Average Annual Incidence of Poliomyelitis in Pregnant and Nonpregnant Women by Age, New York City, 1949-1953.*

the differences in rates associated with previous live births was independent of maternal age.

From the foregoing data, it seems clear that the relative increase in incidence observed in pregnant

women depended on the proportion of such persons with previous live births. In young married women fifteen to twenty-four years of age, 60 to 75 per cent of the pregnancies occurred without previous live births. In older women, the preponderant number had one or more previous live births.[19] The proportion in each group varied progressively with age and affected the incidence in the manner already described.

The results described above were directly related to the presence or absence of children in the household. As expected, there was close similarity between the number of children under eighteen years of age in the households and the number of previous live births. These were exactly alike in 79 per cent of the families. In the others, 14 per cent had more, and 7 per cent fewer children in the household than the number of previous live births. The results observed in pregnancy appeared to be related, therefore, either to household contact with the children or to other factors associated with their presence.

Relation to Gestational Period

There also appeared to be a relation between the occurrence of poliomyelitis in pregnancy and the period of gestation. This can be seen from the data summarized in Table 6 by calendar month of gestation at time of onset of symptoms of poliomyelitis.

TABLE 5. *Average Annual Incidence of Poliomyelitis per 100,000 Person Years in Pregnant Women According to Number of Previous Live Births, New York City, 1949-1953.*

Previous Live Births	Pregnant Person Years	Incidence in All Cases			Incidence in Paralytic Cases			Incidence in Nonparalytic Cases		
		Number	Rate	Adjusted Rate*	Number	Observed Rate	Adjusted Rate*	Number	Observed Rate	Adjusted Rate*
None	268,000	19	7.1	3.0	13	4.9	1.7	6	2.2	1.3
One	234,000	47	20.1	12.8	35	15.0	10.0	12	5.1	2.8
Two or more	184,000	21	11.4	9.1	16	8.7	7.0	5	2.7	2.1
Totals	686,000	87			64			23		
Averages			12.7	8.7		9.3	6.5		3.4	2.1

*Standardized against population of married women of New York City in 1950.

TABLE 6. *Average Incidence of Poliomyelitis per 100,000 Person Years in Pregnant Women by Month of Gestation at Time of Onset of Disease, New York City, 1949-1953.*

Month of Gestation	Pregnant Person Years	Annual Rate for All Clinical Cases		Annual Rate for Paralytic Cases		Annual Rate for Nonparalytic Cases	
		No. of Cases	Rate	No. of Cases	Rate	No. of Cases	Rate
1	82,100	2	2.4	2	2.4	0	0.0
2	82,100	6	7.3	4	4.9	2	2.4
3	82,100	22	26.8	14	17.1	8	9.7
4	74,300	14	18.8	11	14.8	3	4.0
5	74,300	15	20.2	9	12.1	6	8.1
6	74,300	6	8.1	5	6.7	1	1.3
7	72,300	7	9.7	4	5.5	3	4.2
8	72,300	6	8.3	6	8.3	0	0.0
9	72,300	9	12.4	9	12.4	0	0.0
Totals	686,100	87		64		23	
Averages			12.7		9.3		3.4

The number of cases observed varied with the month of gestation. Most of the cases, paralytic as well as nonparalytic, had their onset between the third and fifth months of pregnancy. In this three-month period, 74 per cent of the nonparalytic, and 53 per cent of the paralytic cases occurred. There were a total of 51 cases (59 per cent) in these three months, or an average of 17 cases per month, as against 6 to 8 cases in each of the other months with the exception of the first.

We converted the cases occurring in each month of pregnancy into an incidence rate by dividing by the estimated pregnant population at risk in each month of gestation (Table 6). This was roughly equal to a third of the total person years of gestation estimated for the respective trimesters, as given below under "Severity of Clinical Infection." The data on incidence by month of gestation are shown graphically in Figure 2, and are compared with the expected rates based on the age-specific incidence in the total female population fifteen to forty-four years old. The curve for paralytic cases shows a biphasic trend, with a high level in the third, fourth and fifth months and a sec-

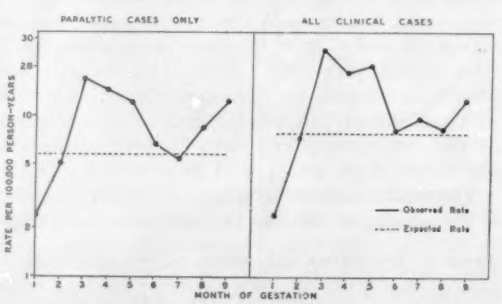

FIGURE 2. *Incidence of Poliomyelitis in Pregnant Women by Month of Gestation, New York City, 1949-1953.*

ondary rise in the last two months. When paralytic and nonparalytic cases were combined only the elevated incidences from the third to the fifth month were apparent.

From the foregoing data it appears that pregnant women were most susceptible to the occurrence of clinical infections toward the end of the first trimester and the beginning of the second. At other times there was no evidence of an increase in susceptibility, with the possible exception of a rise in the eighth and ninth months.

Severity of Clinical Infection

In the analysis of clinical severity that follows, the paralytic cases are subdivided into two broad groups, spinal and bulbar or bulbospinal (bulbar). A summary of the distribution of the 87 cases observed during pregnancy by clinical type and trimester is presented in Table 7.

The proportion of nonparalytic and spinal paralytic cases occurring in each trimester varied, the former decreasing with progression of gestation, and the latter increasing. On the other hand, the bulbar cases were fairly evenly distributed by trimester. At all times they constituted less than 10 per cent of the cases in contrast to a frequency of 21.5 per cent for all females fifteen to forty-four years of age. On the basis of the population at risk, the incidence of bulbar poliomyelitis in the pregnant group was 1.2, whereas the expected rate was 1.7 per 100,000 person years.

There also appeared to be a relation between gestation period and mortality (Table 8). There were only 2 deaths, a case mortality of 3.1 per cent and a mortality of 0.3 per 100,000 person years of pregnancy. This can be compared with a case mortality of 14.9 per cent and a mortality of 0.7 per 100,000 person years in all females of childbearing age. Both deaths occurred in the last trimester, in which the case mortality was 10.5 per cent. The patients who died manifested clinical symptoms in the eighth and ninth months respectively and were the only ones with bulbar paralysis in the last trimester.

TABLE 7. *Clinical Types of Poliomyelitis Observed during Pregnancy.*

GROUP	NONPARALYTIC CASES	SPINAL PARALYTIC CASES	BULBAR PARALYTIC CASES
Pregnant females			
1st trimester	10 (33.3%)	17 (56.7%)	3 (10.0%)
2d trimester	10 (28.6%)	22 (62.9%)	3 (8.6%)
3d trimester	3 (13.6%)	17 (77.3%)	2 (9.1%)
Totals	23 (26.4%)	56 (64.4%)	8 (9.2%)
Total females (15 to 44 yr.)	179 (27.8%)	326 (50.7%)	138 (21.5%)

DISCUSSION

An attempt has been made to measure the incidence and severity of poliomyelitis in pregnancy. Two host factors were considered: maternal age and gestational period. The study was a prospective investigation that began during the epidemic of 1949, when New York City experienced its third largest outbreak, and continued through four succeeding nonepidemic years. It involved a large population of women of childbearing age, most of whom were born in New York City and remained under crowded urban conditions where poliomyelitis recurred each summer and fall with varying force.

The results obtained indicate an increased incidence of poliomyelitis of about 60 per cent in women who are pregnant. The difference in attack rates between pregnant and nonpregnant women rose progressively with age, and became quite marked between twenty-five and thirty-nine years of age.

TABLE 8. *Distribution of Paralytic Cases According to Trimester of Pregnancy.*

GROUP	PERSON YEARS	PARALYTIC CASES	DEATHS	CASE MORTALITY	MORTALITY PER 100,000 PERSON YR.
				%	
1st trimester	246,000	20	0	0.0	0.0
2d trimester	223,000	25	0	0.0	0.0
3d trimester	217,000	19	2	10.5	0.9
Totals	686,000	64	2		
Averages				3.1	0.3
Totals for females (15 to 44 yrs.)	9,728,000	464	69		
Averages				14.9	0.7

The incidence of poliomyelitis in pregnancy and its relation to maternal age have not been thoroughly explored in the past because of the difficulty of obtaining sufficient data. The low incidence of poliomyelitis in the age groups at risk makes it necessary to plan large-scale or long-term community-wide studies to obtain the data required. Since the present study appears to be the first such large-scale prospective investigation to be reported, the results on age-specific rates are not directly comparable with those of other workers. In one study, reference was made to an unpublished investigation in which the occurrence of poliomyelitis in pregnancy was not significantly greater than that of nonpregnant females in the same age groups.[22] However, no specific rates were given. In another study, the percentage of adult females with poliomyelitis who were pregnant at the onset of illness decreased with age, but age-specific rates for pregnant and nonpregnant women were not given.[14]

The relative increase in incidence with maternal age noted in the present study indicated that the results observed during pregnancy were not attributable to pregnancy alone. In the search for an explanation, other factors that varied with maternal age and might influence the results were considered. When the data were analyzed by the number of pre-

vious live births in parturient women, the incidence of poliomyelitis was found to be about three or four times greater in those with previous live births than in those without previous live births. Since the older pregnant women had more previous live births, the increased incidence varied also with age.

The number of previous live births is correlated with the number of children in the household. There was apparently a direct association between the incidence of poliomyelitis in pregnancy and the presence of children in the household. Just how this relation affects incidence is speculative. During the poliomyelitis season, children are readily infected and form a rich reservoir of virus. However, host factors cannot be excluded in the development of the paralytic syndrome.

The differences reported by various investigators obviously reflect variations in conditions that modify the outcome. The importance of this was shown in the foregoing analysis of the results by previous live births. Furthermore, since early pregnancy may be overlooked, all females in the childbearing age must be followed for several months after onset of disease for change in menses and evidence of pregnancy. In the present study, such an investigation increased the number of reported cases in pregnant women by 10 to 20 per cent each year. An increase of this magnitude assumes considerable importance when the differences between pregnant and nonpregnant groups are not marked or on the borderline of statistical significance.

The results observed in the present study do not seem to be attributable to bias arising from differences in reporting or in medical supervision of pregnant and nonpregnant women for a number of reasons. First of all, the increase described applied to paralytic as well as nonparalytic cases. The former are fairly completely reported because of the need for hospitalization and convalescent care. Secondly, the extent of the increase was almost the same for paralytic and for nonparalytic cases. If differences in medical supervision were a factor, one would expect a greater increase in the milder or nonparalytic cases than in the more severe or paralytic cases. Thirdly, the observed increase varied with age and parity. If it were related to bias in medical supervision during pregnancy, one would expect all groups regardless of age or previous live births to be affected equally. Finally, all reported cases were checked by diagnosticians assigned on an area basis without any regard to the age or pregnancy status of the patient.

The occurrence of poliomyelitis in pregnancy appeared to depend, in part, on the period of gestation. A significant increase in incidence of both paralytic and nonparalytic types of cases was observed in the third, fourth and fifth months of gestation only, and was responsible for the over-all rise in incidence reported during pregnancy. A similar concentration of cases between the third and fifth months or in corresponding trimesters was reported in other recent surveys.[5,6-7,10,14] The explanation for the apparent increase in susceptibility during this period of gestation is not entirely clear. It may be related to hormonal changes, which have been shown to modify host susceptibility in the laboratory animal.[23-26]

Differences in severity of infection that appeared to be of epidemiologic and prognostic significance were also noted. The increase in paralytic cases observed during pregnancy appeared to be limited to the spinal type of disease. It was noted in the second and third trimesters only, particularly in the last, and affected chiefly the lower limbs. It was not accompanied by a parallel increase in bulbar or bulbospinal paralysis. On the contrary, the frequency of bulbar poliomyelitis appeared to be equal to or less than that expected in every trimester and age group. The over-all reduction in bulbar paralysis was about 30 per cent. In studies reported by several other investigators, the proportion of bulbar cases also appeared to be either comparable to or lower than that observed among cases in nonpregnant persons.[4,6,14] Since deaths occur most commonly in bulbar cases, it is not surprising that the mortality rate was reduced in pregnant women. Only 2 deaths occurred, both in the last months of pregnancy.

Summary

The incidence of poliomyelitis during pregnancy was investigated in New York City in a prospective study of all cases reported in females fifteen to forty-four years of age for a five-year period from 1949 to 1953, inclusive.

A total of 87 cases were observed in pregnant women. This number was 59 per cent more than that expected on the basis of age-specific rates in the female population of childbearing age. The percentage increase in clinical infections noted during pregnancy was the same for paralytic and nonparalytic cases.

The attack rate of clinical infection was higher in pregnant women with previous live births than in those without previous live births. A relation between parity and the incidence of poliomyelitis in pregnancy was observed in each maternal age group, and appeared to be dependent, in part, on the number of children in the household.

The incidence of clinical infection also varied with the period of gestation, being increased only in the third, fourth and fifth months, and possibly in the last month of pregnancy.

The increase in incidence during pregnancy appeared to be limited to nonparalytic and spinal paralytic cases, whereas the frequency of bulbar cases seemed to be reduced. Mortality, therefore, was also reduced. Only 2 fatal cases occurred, both in the last trimester of pregnancy.

We are indebted to Mr. Carl Erhardt, director, and Mr. Louis Weiner, chief of the Statistical Division, Bureau of

Records and Vital Statistics, New York City Health Department, for the data from the 1950 census and on the annual number of reported live births and fetal deaths.

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CHEMICAL AND HISTOCHEMICAL SEQUENCES IN THE NORMAL HEALING OF WOUNDS*

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BOSTON

THE healing wound is of perennial interest and fundamental importance to the surgeon. Despite continued study, however, knowledge to date consists largely of the factors that affect the well known histological sequences of healing and the rate of gain in tensile strength. The intensive inquiries[1,2] that many investigators have conducted into the nature of connective tissue in the last decade have provided a variety of technics, some old and some new, that require application to the healing wound. This report reappraises the sequences of wound healing on the basis of data obtained from chemical and histochemical studies.

Formation of Collagen

An understanding of certain facts regarding the nature of collagen and its formation is germane to the problem under consideration. At one time it was believed that the fibers were shed from the superficial protoplasm of the fibroblast and incorporated directly into tissue as collagen. Others have held that collagen is precipitated from the ground substance without any need for cellular activity. The studies of Stearns[3,4] on fibrogenesis in the ear of the rabbit indicate that fibroblasts are essential for fiber formation, but by contributing material that ultimately results in collagen rather than by producing it directly. More recently the nature of this process has been clarified to some extent. Porter and Vanamee,[5] using the electron microscope, observed an interaction between fibers laid down on either side of the cellular membrane and materials in the ground substance. Highberger,[6] from in vitro studies, has shown that a dialyzed acid solution of collagen can be made to precipitate into a collagen fiber in the presence of an acid polysaccharide such as chondroitin sulphuric acid.

From these studies one may postulate that fibroblasts secrete a soluble protein procollagenous substance that is essential to fiber formation, but that the process is not complete without the presence in tissues of a carbohydrate fraction in the ground substance. The nature of ground substance and its relation to the blood, to mast cells and to the ultimate appearance of mucopolysaccharides need not be discussed in detail in this paper. Briefly, there are two opinions regarding the origin of the mucopolysaccharides of the ground substance. One has held that it is secreted by fibroblasts[7,8] whereas the other maintains that it is a product of mast cells.[9] Time and further study may yet resolve this controversy by showing that what appear to be mast cells are actually young fibroblasts. Whatever the exact source of ground substance, it seems likely that some fraction

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of the mucopolysaccharides, probably a sulfated acid polysaccharide, provides a medium in which procollagen is converted to collagen. There is considerable evidence that ascorbic acid is essential to this change.

In summary, then, the ultimate formation of collagen, which provides tensile strength to a wound, is dependent upon two factors: a protein component, probably produced by fibroblasts, which passes through several stages before becoming collagen; and a carbohydrate component, — a complex mucopolysaccharide produced either by mast cells or connective-tissue cells, — which produces a homogeneous matrix that is chemically and physically necessary for the ultimate deposition of adult collagen from the soluble, nonfibrous protein material produced by the connective-tissue cells. Ascorbic acid and a variety of enzyme systems are undoubtedly involved in this process.

TABLE 1. *Glucosamine in Healing Wounds.*

SPECIMEN	GLUCOSAMINE CONTENT*
	mg./100 gm. of dry tissue
Normal skin	450
3-day wound	956
6-day wound	790
9-day wound	505
12-day wound	475
15-day wound	466

*Mean of 3 or more determinations; variations so small as to be statistically insignificant.

In this study we have attempted an elucidation of the mechanisms of healing by measuring the sequential formation of mucopolysaccharides and collagen in the wound.

MATERIAL AND METHODS

The healing of the normal wound has been studied in healthy rats of the Wistar strain weighing between 200 and 250 gm. Wounds were made in the abdominal cavity and closed with interrupted wire sutures. The wires were removed before the wounds were sectioned for histologic and histochemical examination. Chemical determinations of healing tissue were made in open granulating wounds on the back of the animal. Great care was taken to include only granulating tissue in the assay.

The presence of mucopolysaccharides was determined, first, by metachromatic staining with toluidine blue as described by Sylvan[10] (there is considerable evidence that this technic depends on the presence of free sulfate groups attached to the polysaccharides); secondly, by the colloidal-iron technic of Hale[11] as modified by Reinhart and Abul-Haj[12]; thirdly, by the periodic acid Schiff stain, as described by Hotchkiss[13] (although there is considerable controversy about the nature of this stain, it is sufficiently specific for our purposes to indicate the presence of a carbohydrate fraction in tissue); and, finally, by the Elson and Morgan chemical analysis for hexosamines as used by Persson.[14]

Collagen formation was evaluated histochemically by van Gieson's and Mallory's stains. Precursors of collagen such as reticulin were estimated by silver stains, particularly Gomori's silver-impregnation technic. The hydroxyproline content of tissue was used as a chemical assay for collagen. The method of Neuman and Logan[15] was employed.

Histologic and histochemical preparations were made from animals killed three, six, nine and twelve days after operation. Chemical determinations were made of granulating tissue removed from open wounds on the third, sixth, ninth, twelfth and fifteenth days after operation.

Histochemical changes have been established in a rough way by the use of plus signs (+). The faintest trace of a staining reaction was recorded as +. The most intense reaction over the period of study was recorded as ++++.

RESULTS

The results are presented in Tables 1 and 2 and in Figures 1, 2, 3 and 4. In Figure 5 the data on hexosamine and hydroxyproline content of the healing wound are superimposed on a empirical curve of gain in tensile strength. Since tensile strength could not be determined in the same animals, this is projected upon the basis of other studies.

The data may be briefly summarized. During the early stages of wound healing, in the so-called lag period, there is a rapid increase in hexosamine content of the wound. Although there is no gain in tensile strength, it is evident that marked changes are taking place in the ground substance. Toluidine blue stain for metachromasia, the periodic acid Schiff and Hale's colloidal iron stain all become positive during this early period, presumably indicating the presence of mucopolysaccharides (Fig. 1). Metachromasia is of particular interest because it reaches a peak about the fifth or sixth day, when the first chemical and histologic evidence of collagen fibers develops. As collagen forms there is a prompt decline in metachro-

TABLE 2. *Collagen* in Healing Wounds.*

SPECIMEN	COLLAGEN CONTENT†
	%
Normal skin	71.9‡
3-day wound	8.8
6-day wound	9.9
9-day wound	22.3
12-day wound	31.3

*Collagen = hydroxyproline per 100 gm. of dry tissue × 7.46.
†Mean of 3 or more determinations; variations so small as to be statistically insignificant.
‡After Bowes & Kenton.[16]

masia and a progressive fall in the hexosamine content of the wound (Fig. 1, 2 and 3). Toward the end of the period of fibroplasia, as the wound approaches maximal tensile strength, the degree of metachromasia and the intensity of the colloidal iron stain return to the levels seen in normal skin and subcutaneous tissue. On the other hand, the periodic acid Schiff stain remains positive into the period of cica-

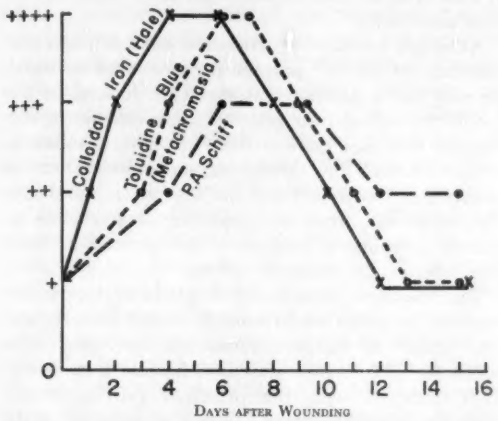

FIGURE 1. *Histochemical Estimation of Mucopolysaccharides in the Healing Wound.*

trization. Whether this indicates the presence of a carbohydrate fraction of the mucopolysaccharide incorporated into collagen or whether it is related in some way to hydroxyproline has not been determined.

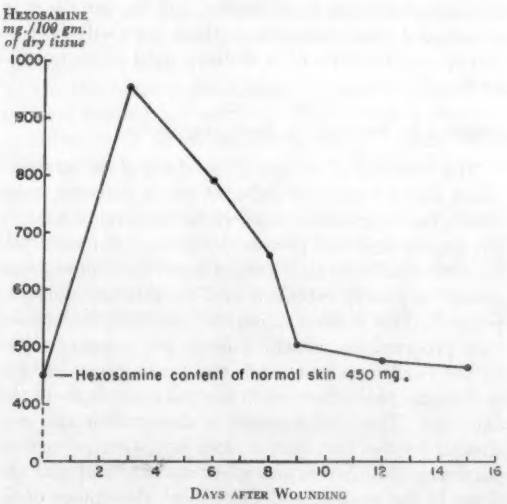

FIGURE 2. *Hexosamine Content of the Healing Wound.*

The interrelation between reticular staining material (Gomori's stain) and the formation of collagen as estimated by van Gieson's stain is depicted graphically in Figure 4.

There is a remarkably good correlation between the gain in tensile strength and the appearance of collagen both as seen histologically and as measured by the

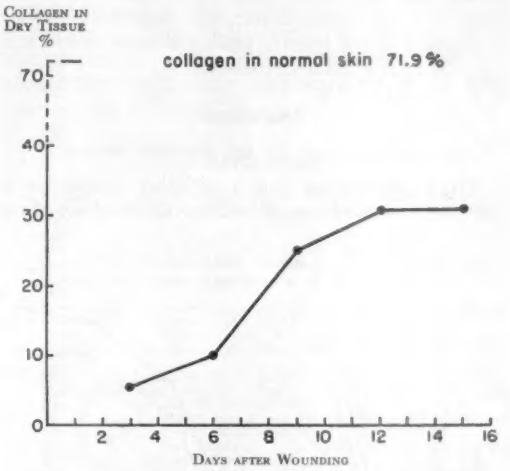

FIGURE 3. *Collagen Content of the Healing Wound.*

hydroxyproline content of the tissue. Although the maximal rises in hydroxyproline content are a little delayed, it seems likely to us that the early initial gain in tensile strength is due to the presence of some col-

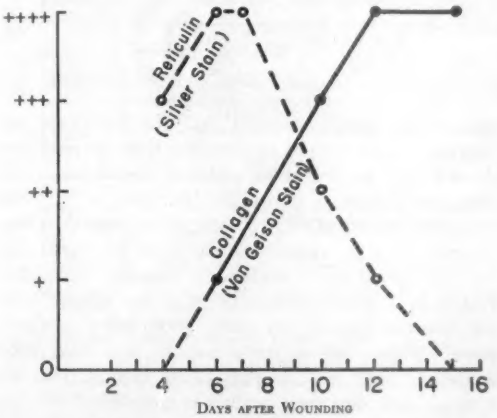

FIGURE 4. *Histologic Estimation of Reticulin and Collagen in the Healing Wound.*

lagenous or procollagenous material because during the lag phase, when a large quantity of mucopolysaccharide is present, there is little or no gain in tensile strength. Studies on scorbutic guinea pigs, which will be described in detail elsewhere, lend support to this view also.

It will be noted that the curve of gain in hydroxyproline content of the tissue levels off after the twelfth to the fourteenth day. This is in contrast to the observations of Abercrombie et al.,[20] who found a progres-

sive rise in hydroxyproline for as long as the twenty-fifth day. We believe that this is due to the fact that their determinations were made on wet tissue. Since edema fluid is absorbed from the wound between the tenth and the twentieth day, one may obtain a false impression of the hydroxyproline content unless it is measured per gram of dry tissue.

Discussion

"Pattern of Healing" in the Normal Wound

These observations give a different perspective to the mechanisms of wound healing. On the basis of the changes in tensile strength and the histologic appearance alone wound healing has been divided into three stages: an initial lag phase of one to four days' duration; a phase of fibroplasia from four to ten days; and a final phase of cicatrization, of variable duration, depending on the amount of scar tissue produced during healing. If one considers the changes depicted in Figure 5, it seems reasonable to divide wound healing into two phases: an early "productive" or "substrate" phase lasting from one to five days after wounding; and a "collagen" phase lasting from the fifth or sixth day until healing is complete.

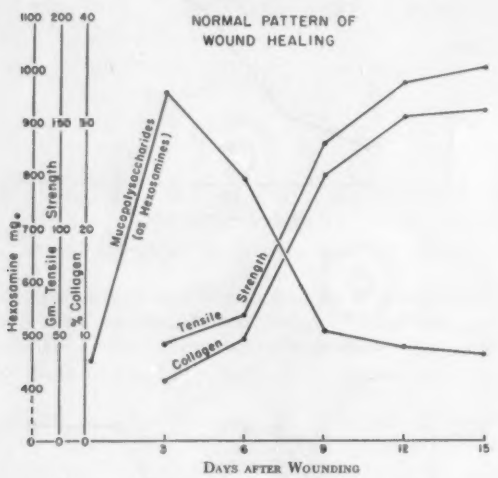

FIGURE 5. *Normal Pattern of Wound Healing.*

Considerable attention has been given to the "lag phase" of healing, and various means of shortening it have been sought unsuccessfully. In general this period has been regarded as comparatively static, being concerned largely with the absorption of débris and dead cells. Harvey,[21] in his Judd Lecture, says, "It is involved in the cleaning up process of the wound." Needham[22] speaks of the period of "defense and demolition." Autolysis and phagocytosis have been thought to be the dominant cellular activities during this period.

Our observations indicate that after an initial period of "shock" of no more than twelve to twenty-four hours' duration there is a rapid production of ground substance that reaches a peak somewhere between the third and the sixth day. Since this homogeneous metachromatic matrix is probably produced by fibroblasts,[8] it is obvious that this is an early function and does not require the presence of the large number of fibroblasts that appear in the wound late in the period of fibroplasia, when the amount of ground substance as measured chemically and histochemically appears to be decreasing.

Although we have no chemical data to prove the existence of soluble protein precursors of collagen, we may safely assume that these are formed in the productive or substrate phase because reticular silver-staining fibers are demonstrable in significant quantities by the sixth day. Moreover, some observations of Gould and Woessner[22] indicate that glycine and proline, which constitute the important amino acids involved in collagen formation, are present in large quantities in the productive phase.

The so-called periods of fibroplasia and cicatrization can be better understood if viewed as early and late phases of collagen formation extending from about the fifth or sixth day until healing is complete. This coincides with the principal gain in tensile strength. Since fibroblasts can be demonstrated in the wound within twenty-four hours of injury it seems likely that tensile strength, which does not increase until the fourth to the sixth day, is largely a result of collagen synthesis rather than simple multiplication of fibroblasts as has been assumed.

Further confirmation of these concepts can be derived from a study of delayed or abnormal wound healing. Although these studies will be described in detail later, brief reference to them here will serve to clarify our concept of a distinct pattern to normal healing.

"Pattern of Healing" in Deficiency States

The concept of an initial productive or substrate phase and a second or collagen phase becomes more intelligible when one considers the pattern of healing in ascorbic acid and protein deficiency. For example, in wounds in scorbutic guinea pigs* the "productive phase" is greatly extended and there is no "collagen phase." The concentration of mucopolysaccharides rises progressively, reaching levels per gram of tissue by the twelfth or fourteenth day far in excess of that seen at the peak observed in normal wounds about the fifth day. That this material is abnormal is also evidenced by the fact that it does not stain metachromatically. Much reticular silver-staining material appears in the wound, and there is an abundance of fibroblasts. However, very little collagen can be seen by Mallory's or van Gieson's stains, and very little hydroxyproline can be demonstrated. In less than forty-

*Although there is a slight difference in the absolute quantities of hexosamines and hydroxyproline that can be found per gram of tissue in the rat and guinea pig, the relative changes after wounding are remarkably similar.

eight hours, however, after the administration of ascorbic acid such a wound will pass into a "collagen" phase in which hydroxyproline can be found in appreciable quantities and well formed collagen fibers can be demonstrated by staining technics. It appears that in ascorbic acid deficiency the building blocks of wound healing are produced plentifully in the productive phase, but an important key to synthesis of collagen is lacking.

If a rat is fed a nonprotein diet for a period of five days before wounding, the pattern of healing differs from both the normal one and that seen in scorbutic guinea pigs. The productive phase is prolonged, and the peak levels are below normal. This is followed by a collagen phase, which does not begin until the seventh or eighth day and progresses more slowly than normal. The pattern of healing seems to be one of a deficiency of building blocks as well as delayed formation of collagen. It has been known for some time that the defective healing of wounds in protein deficiency can be restored to normal by administration of methionine, and it is of particular interest that the pattern of healing, as measured by chemical and histochemical technics, can also be shifted toward normal simply by the addition of methionine to the diet. Whether methionine acts by supplying an essential building block or by contributing to more rapid utilization of body protein, as Localio, Morgan and Hinton[24] have suggested, is a question that is being studied further.

Summary and Conclusions

The sequential formation of ground substance and collagen in the normal healing wound in the rat and guinea pig as estimated by chemical and histochemical technics is described.

On the basis of these data a "normal pattern" of wound healing is described. This has two phases: a productive or substrate phase, which begins shortly after wounding and lasts for about five days (during this period mucopolysaccharides and soluble protein precursors of collagen, the building blocks of repair, are produced); and a collagen phase, in which normal collagen fibers are formed (this begins about the fifth day and lasts until the completion of healing).

In this concept there is no "lag phase" to wound healing, and normal tensile strength is a function of collagen formation not of fibroblastic multiplication as formerly postulated.

Under the condition of these experiments the pattern of wound healing in protein and ascorbic acid deficiency is distinctly abnormal. Further studies of the pattern of healing in these and other conditions should lead to a better understanding of the basic mechanisms of repair.

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CLINICAL VALUE OF A TRACING OF FORCED EXPIRATION (EXPIROGRAM)*

II. Cardiac Disease

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THE clinical application of a kymographic record of a maximal expiration (expirogram) in the diagnosis and management of pulmonary disease was discussed in a previous paper, in which the advantages of tracings over other means of obtaining the so-called "timed capacity" were pointed out.[1] We are presenting evidence here that such tracings are also of value in the management of cardiovascular disease.

The congestion of the pulmonary vascular bed in left-sided heart failure causes a decrease in the vital capacity.[2-4] However, little attention has been paid to associated changes in the speed of expiration, which is also often altered in a characteristic manner in chronic cardiac failure.

MATERIALS AND METHODS

The apparatus, previously described,[1] consists of a 6-liter spirometer, the bell of which is connected to a pen recording on a kymograph moving at 0.56 cm. per second. Three groups of patients were selected for study: patients with hypertensive heart disease who, on the basis of the usual clinical criteria, were considered to be in congestive heart failure; patients with mitral stenosis, with or without existing congestive heart failure; and patients with chronic pulmonary disease and resulting or associated heart failure. Some of the patients in all three groups were observed for several weeks to determine the effect of treatment of the congestive heart failure on the configuration of the expirogram.

RESULTS

Group 1

The following case is typical of the first group of patients with congestive heart failure secondary to hypertensive heart disease.

W.B., a 49-year-old man, was admitted to the hospital on December 29, 1954, with a chief complaint of progressive dyspnea, orthopnea and ankle edema. Hypertension had been present for 5 years, but he had remained symptom free until 1951, when he experienced chest pain and a diagnosis of coronary-artery disease with angina pectoris was made at another hospital and subsequently confirmed by the "2-step" test. In 1953 symptoms of dyspnea on exertion, paroxysmal nocturnal dyspnea and minimal ankle edema were treated successfully with digitalis, and he was given various drugs for hypertension. Three months before admission, digitalis was stopped because the pulse rate was 40 per minute. Progressive dyspnea, orthopnea and swelling of the ankles then developed for the 2d time.

On admission he was pale and in moderate respiratory distress, with marked swelling of the lower legs. The temperature was 99°F., the pulse 60, and the respirations 28. The blood pressure was 220/130. The neck veins were distended, and there was fullness to percussion, decreased breath sounds and moist inspiratory rales in the lower two thirds of the chest posteriorly. The heart was enlarged, the border extending to the midaxillary line. The pulmonic 2d sound was split, and the aortic 2d sound was greater than the pulmonic; there was a Grade 2 apical systolic murmur and a diastolic gallop. The liver edge was tender and palpable 10 cm. below the right costal margin. Marked pitting edema was present to the level of the 12th thoracic segment posteriorly. The venous pressure was equivalent to 14 cm. of water, and the arm-to-tongue circulation time was 30 seconds. X-ray examination of the chest showed cardiac enlargement and pulmonary congestion. The hemoglobin was 10.5 gm. per 100 cc., the hematocrit 39 per cent, and the white-cell count 4000, with a normal differential. The blood urea nitrogen was 40 mg., and the creatinine 2.6 mg. per 100 cc. The blood carbon dioxide, chloride, sodium and potassium were normal. An electrocardiogram was interpreted as showing strain of the left ventricle.

The patient was treated with digitalis, ammonium chloride, mercurial diuretics by injection and a preparation containing *Rauwolfia serpentina* and *Veratrum viride* derivatives. There was great clinical improvement in 10 days, and the circulation time fell to 17 seconds.

On the day after admission the vital capacity was 1900 cc., with 1600 cc. expired in the 1st second. Three days later the vital capacity was 2600 cc., with 2200 cc. in the 1st second, and 3 days later it was 2900 cc. Subsequent measurements showed further increases in both volume and in speed, and on discharge the vital capacity had risen to 3000 cc., with 2600 cc. expired in the 1st second. The patient was given a ganglionic-blocking agent and discharged to be followed in the outpatient department.

Figure 1 shows the expirogram of this patient and 2 others with hypertension and congestive heart failure, with the predicted normal tracings of each. The expirogram of this group has certain characteristics. The rate of expiration is relatively rapid although the total volume expired is reduced. The reduction in vital capacity is reversible partially or wholly after treatment of the congestive heart failure. The administration of a bronchodilator by aerosol does not increase the rate of expiration, nor did this or less forceful expiration increase the vital capacity, as shown in Figure 2.¶

Group 2

The second group of patients studied were those with chronic congestive heart failure secondary to mitral disease. The following case is illustrative.

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¶The influence on the expirogram of the force with which the patient expires has been discussed.[1]

C.J., a 43-year-old housewife, was admitted to the hospital on December 28, 1954, because of difficult breathing of 2 days' duration. At the age of 9 years she had had migratory arthralgia and a grippelike illness. At 21 years of age, during her 1st pregnancy, a heart murmur was discovered. During a subsequent pregnancy a diagnosis of rheumatic heart disease and mitral stenosis was made, and treatment with digitalis was started. She remained well until 1942 (age 31 years), when progressive weight gain, dyspnea and orthopnea developed. Symptoms persisted, and in 1952 a valvuloplasty was done after cardiac catheterization, with good symptomatic relief despite a persistently elevated pulmonary capillary pressure postoperatively. During the year before the present admission there had been moderate dyspnea, especially on exertion, despite continued digitalis and mercurial diuretics given intermittently by injection. Two days before admission she became more dyspneic than usual, with a hacking cough that became productive of mucoid sputum on the day of admission.

Examination revealed a thin, orthopneic woman with cyanosis and distended neck veins. The temperature was

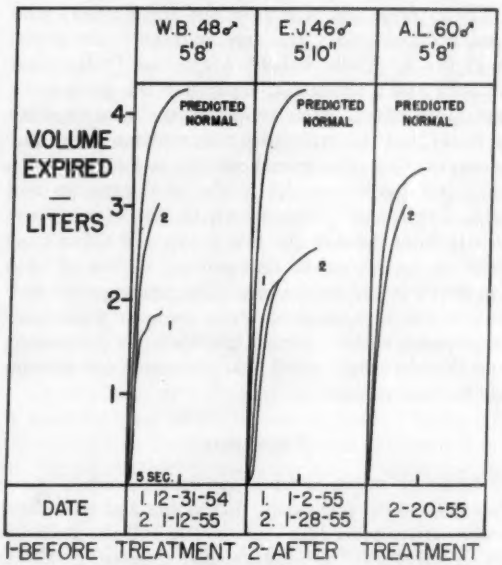

FIGURE 1. *Expirogram of W.B., Compared with Those of 2 Other Patients with Hypertension and Congestive Heart Failure.*

Predicted normal tracings are also shown.

99.8°F., the pulse 112 and irregular, and the respirations 34; the blood pressure was 108/80. Breath sounds were decreased, and there were fine, moist rales at both bases. The left border of cardiac dullness and the point of maximal impulse were at the anterior axillary line. A presystolic thrill and shock were present at the apex, and a systolic thrill was present in the pulmonic area. There was a Grade 2 diastolic decrescendo murmur at Erb's point and a Grade 3 rough systolic and diastolic murmur at the apex. The pulmonic 2d sound was accentuated. The liver edge was palpable 4 fingerbreadths below the right costal margin and nontender. The spleen was palpable.

The hematocrit was 56 per cent. The sedimentation rate was normal. The white-cell count was 14,500. The urine had a specific gravity of 1.020 and gave a ++++ test for albumin. There were 20 to 30 white cells and 3 to 5 red cells per high-power field in the sediment. The blood urea nitrogen was 26 mg. per 100 cc. Blood cultures were negative. An x-ray film of the chest revealed transverse enlargement of the heart, prominence in the region of the pulmonary artery, an increase in the hilar vascular markings and a hazy infiltrate in the region of the right hilus. An electrocardiogram showed atrial fibrillation and strain of the right ventricle.

The patient was given a low-salt diet, aqueous penicillin, 200,000 units intramuscularly every 4 hours, digitalis leaf, 0.20 gm. daily, and mercurial diuretics by injection. She was discharged considerably improved on the 15th hospital day.

The expirogram of this patient and those of 5 others with mitral stenosis are shown in Figure 3. As

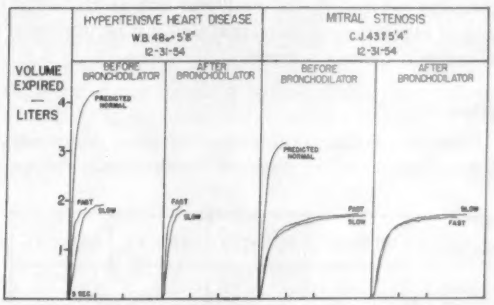

FIGURE 2. *Effect of Bronchodilators on the Expirogram in Heart Disease.*

in the previous group, the vital capacity is decreased. The configuration of the curves, however, differs from the first group in that, although the initial portion is steep, there is marked flattening of the terminal portion of the tracing. In spite of an increase in the vital capacity as the patient improves clinically under treatment, this flattening of the tracing persists.

The configuration just described is quite different from that obtained from normal persons. During a maximal forced expiration, it has been shown that

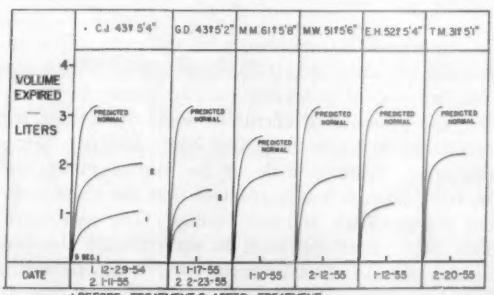

FIGURE 3. *Expirograms in 6 Cases of Mitral Stenosis.*

the normal lung empties in a regular manner. This becomes evident if the expirogram is recorded on paper moving sufficiently fast (3 cm. per second) to permit accurate measurement of the volume that has been expired at each instant during the entire expiratory effort.[5] If the volume remaining to be expired at any instant is plotted on a logarithmic scale and time is plotted arithmetically, a straight line is obtained. This means that the rate of expira-

tion decreases in a predictable manner and that if the total volume expired is known and the volume expired in the first second, for example, is also known, the entire curve can be reconstructed. Patients with asthma or emphysema often exhibit irregularities in the manner in which the rate of expiration changes. The abrupt slowing toward the end of expiration seen in Figure 3 represents such an irregularity. Furthermore, these curves deviate most strikingly from the normal at the end and not at the beginning of expiration, a point that will not be appreciated unless a tracing is made.

Group 3

Because cardiac failure and chronic pulmonary disease have certain features in common, the two

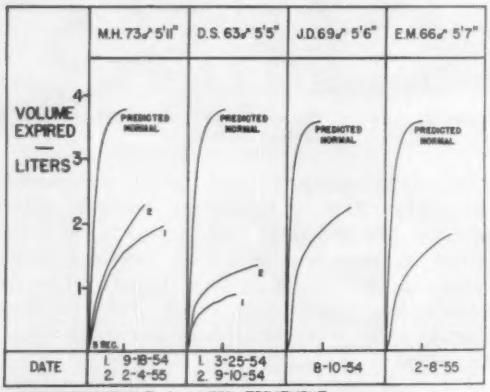

FIGURE 4. *Expirograms in 4 Cases of Pulmonary Emphysema and Congestive Heart Failure.*

are sometimes distinguished with difficulty. One encounters patients with a chief complaint of dyspnea who, because of a known cardiac lesion, hypertension, the presence of edema or some other sign, are considered to have congestive heart failure. Treatment may produce little or no improvement, and the conclusion is finally reached that the chief problem is pulmonary and not cardiac. The two conditions may occur together; in such a case the pulmonary disease must be recognized if the patient is to receive optimal care. As the following case illustrates, the expirogram can readily detect the presence of pulmonary disease in such patients and thereby help to guide the physicians in the management of the patient.

M.H., a 73-year-old man, entered this hospital for the 2d time on August 27, 1954, with a chief complaint of severe dyspnea of 4 to 6 weeks' duration. Eight years previously he began to have increasing shortness of breath and a productive morning cough. Two years later he retired from work because of persistent dyspnea even at rest. There had been ankle edema for 1 year before admission. Examination revealed a chronically ill, emaciated, cyanotic, elderly man who was breathing with much difficulty. There was increased anteroposterior diameter of the chest, prominence of the ribs and flaring of the lower costal margin, especially on the left. The lungs were hyper-resonant, and there were inspiratory rales at both bases, with wheezes throughout. The liver edge was palpable 4 fingerbreadths below the right costal margin, and there was moderate ankle edema. Complete situs inversus was present. The hematocrit was 55 per cent, the hemoglobin 16.3 gm. per 100 cc., and the sedimentation rate 8 mm. per hour; the white-cell count was 8650. The urine was normal. The blood carbon dioxide was 36.2 milliequiv. per liter. An electrocardiogram showed right-bundle-branch block. An x-ray film of the chest revealed increased bronchial markings, especially on the left. The arm-to-tongue circulation time was 15.5 seconds, and the venous blood pressure was equivalent to 10.9 cm. of water.

The patient was given a low-sodium diet, digitalis, bronchodilator drugs, expectorants and mercurial diuretics. His state remained relatively unchanged until treatment with cortisone was begun on the 7th hospital day, after which there was marked improvement, with an increase in the vital capacity from 1900 to 2600 cc.

The expirograms of this patient and 3 others with combined pulmonary and cardiac diseases are shown in Figure 4. There is both a decrease in the vital capacity and a slowing of expiration throughout the expiratory effort. After treatment the vital capacity increases, but the expiratory rate remains slow. The administration of a bronchodilator is followed by a small but significant rise in the vital capacity and rate. Expiratory tracings seen in this group differ clearly from those of the first group and differ from those in the second in that slowing is present from the beginning of expiration. The prolonged expiratory curve is typical of those seen in pulmonary emphysema without clinically evident cor pulmonale, and therefore right-sided heart failure is not detectable by this means.

Discussion

Although much of what has been described above has been noted previously, this simple and we believe informative procedure has received little attention as an aid in the diagnosis and management of cardiac disease. As pointed out earlier[1] the kymographic tracings of maximal forced expiration, though even more useful in pulmonary disease, have been passed over in favor of a far more cumbersome and stressful procedure, the maximum breathing capacity, poorly tolerated and often resented by the patient. Our purpose here is to call attention to a useful procedure that is quickly done, requires no sustained effort and lends itself to ready interpretation.

The decrease in vital capacity associated with congestive heart failure has been ascribed to an alteration in the elastic properties of the lung, with resultant increase in resistance to motion.[6] If failure is of long standing, changes, presumably irreversible, take place in the lung; these include capillary dilatation, an increase in thickness in capillary basement membranes and separation of the capillaries from the alveoli by interstitial edema, deposition of collagen and finally, in some cases, by disappearance of capillaries. These changes are limited to the pericapillary alveolar area,

with little involvement of bronchial elements.[7] In the absence of emphysema, asthma or pulmonary edema,[8,9] the rate of airflow at the beginning of expiration is not greatly reduced. One may explain the configuration of the expirograms obtained from patients with chronic congestive heart failure by assuming the presence of an unobstructed airway and a relatively rigid and nonelastic lung. This last can account for both the decrease in vital capacity and the marked and abrupt slowing that occurs as the terminal 100 to 200 cc. are expired. This was first noted by Cournand et al.[10] and is clearly depicted in Figure 3.

The relatively rapid expiratory rate observed throughout expiration in patients with congestive heart failure of short duration, and during the greater part of expiration in patients with chronic congestive heart failure, affords a ready means of distinguishing between cardiac failure and pulmonary emphysema or severe asthma. Since these diseases have, in common with cardiac failure, dyspnea as their most prominent manifestation, the presence or absence of obstruction to the airway, easily recognized by means of the expirogram, may provide a much needed clue to the nature of the disease. During expiration early slowing is easily detected in bronchial obstruction with timed capacity measurements, but the late slowing in chronic congestive heart failure will only be evident when measurements are made at varying intervals. This will require repeated efforts by the patient. A tracing requiring a single effort gives even more information.

On the basis of a limited number of observations it appears likely that chronic congestive heart failure of the type associated with mitral stenosis will not be distinguishable from pulmonary fibrosis on the basis of the expirogram alone because the same factors appear to operate in both conditions. However, when the other clinical features are taken into account, confusion between the two will not arise frequently.

Summary and Conclusions

The application of a kymographic tracing obtained during the measurement of the vital capacity in the diagnosis and treatment of patients with cardiac disease is discussed. The vital-capacity determination alone is well known to be helpful in proper management and control of such patients. Inclusion of a measure of the speed of airflow during performance of the vital capacity is far more informative than the vital capacity alone or than recordings of volumes expired during arbitrarily selected intervals.

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CONGENITAL TRACHEOESOPHAGEAL FISTULA WITHOUT ESOPHAGEAL ATRESIA*

Report of a Case with Post-Mortem Findings

Charles V. Pryles, M.D.,† and Andrew Huvos, M.D.‡

BOSTON

THE presence of a fistulous communication between the esophagus and trachea, without an accompanying esophageal atresia, is rarely reported and is not familiar to many physicians. The classification of congenital anomalies of the esophagus with tracheoesophageal fistula, as reported by Vogt[1] and Ladd and Swenson,[2] is known to most pediatricians.

A brief historical review of this unusual type of anomaly has been published.[3] Recently, in a review of the English literature, Ware and Cross[4] were able to find 26 cases, to which they added 1 of their own. We could find only 10 cases with reported post-mortem findings. In 1917 Cautley,[5] reviewing the literature up to that date, mentioned the existence of 6 such case reports. However, more recently, Haight,[6] in reviewing the original references given by Cautley, could verify only 3 cases that could be classified as tracheoesophageal fistula without atresia of the esophagus. In 1923 Lohnes[7] presented the post-mortem findings in a nine-week-old boy, who, in addition to the tracheoesophageal fistula, had heterotopic pancreatic tissue in the wall of the stomach.

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Six years later Negus[8] described a case of congenital tracheoesophageal fistula, verified by autopsy, in a forty-five-year-old man who died of bronchogenic carcinoma. Gengenbach and Dobos,[9] in 1941, reported the autopsy findings in a three-month-old girl who was found to have fusion of the two kidneys on the left side and a patent ductus arteriosus in addition to the tracheoesophageal fistula. In 1950 Cardullo and Berens[10] described the post-mortem

FIGURE 1. *Posterior View of the Esophagus.*
The posterior wall has been opened longitudinally, and a probe inserted into the fistulous communication between the esophagus and trachea. Note the uniform diameter of the esophagus throughout its length.

findings in an eight-month-old girl with tracheoesophageal fistula who died of bronchopneumonia postoperatively. In the same year Ferguson[11] presented 2 autopsied cases of tracheoesophageal fistula without atresia of the esophagus; 1 patient, a nine-day-old girl, died postoperatively of bronchopneumonia, and the other, a seven-and-a-half-month-old girl, died on arrival at the hospital.

It is our belief that this anomaly, described so rarely, has certain clinical characteristics that merit emphasis if corrective surgery is not to be unduly delayed. It is for this reason that we are reporting an illustrative case in detail, including findings at post-mortem examination.

CASE REPORT

B.S., a 4-day-old girl, was admitted to the Pediatric Service on October 6, 1954. She had been delivered at term, without complication, at another institution. The birth weight was 2.8 kg. (6 pounds, 4 ounces), and the prenatal history was not remarkable. From birth an unusually large amount of mucus in the pharynx and mouth was noticed. Oral feedings were withheld, and small amounts of fluid were administered parenterally. On the 3d day of life, under fluoroscopic examination, the infant was given a swallow of Lipiodol, which was observed to pass freely into the stomach. Immediately after this, regurgitation and aspiration occurred, and films taken at this time showed the outline of a normal esophagus and tracheobronchial tree. It was believed that the existence of a tracheoesophageal fistula of the H type could not be excluded, and the infant was transferred to the Boston City Hospital for further observation and study.

On admission the patient weighed 2.4 kg. (5 pounds, 3 ounces). There was a thick, frothy, mucoid discharge from both nostrils. Coarse rhonchi were heard diffusely over both lung fields. The abdomen was distended and tympanitic; peristalsis was active.

The temperature was 105°F., and the pulse 140, and the respirations, accompanied by flaring of the nares, were 48.

Routine laboratory studies were normal except for a moderate leukocytosis and a slight neutrophilia. The blood was Type O and Rh positive. Cultures of the nose and throat grew *Aerobacter aerogenes,* hemolytic *Staphylococcus aureus,* enterococcus and *Neisseria catarrhalis.* A blood culture was negative. Examination of the stools showed normal tryptic activity. Roentgenograms of the chest revealed an abnormal density involving the upper two thirds of the right-lung and the upper half of the left-lung field. Under fluoroscopy, a No. 10 catheter was passed to the upper part of the esophagus, and Lipiodol, introduced through the catheter, was seen to pass freely into the stomach. No fistula was visible in the prone, supine or lateral position. It was decided to delay further studies until the patient's condition had been stabilized.

She was placed in an incubator, with the lower extremities elevated and the head dependent to facilitate drainage from the pharynx. Feedings were given by gavage. Suction of the pharynx was done as necessary, and humidified oxygen was administered. Penicillin and streptomycin were given intramuscularly. Hydration was maintained by subcutaneous clyses.

The temperature fell to normal within 36 hours, and remained so throughout the hospital stay. It was noted that whenever the patient lay on her back the abdomen became distended, and respiratory distress with cyanosis ensued. She appeared more comfortable in the prone position. Physical examination and x-ray study of the abdomen showed no intra-abdominal disease to account for the distention.

On the 4th hospital day, a loud systolic murmur was heard for the 1st time over the entire precordium, with greatest intensity in the 3d left interspace. The heart was not enlarged, and an electrocardiogram was normal.

The gavage feedings were usually tolerated very well. On occasion the patient became restless after feeding, and abdominal distention, gagging and cyanosis occurred; prompt suction with removal of mucus afforded relief. The presence of much mucus in the mouth and pharynx was noted by several observers. Such episodes necessitated the discontinuance of gavage feedings and the maintenance of hydration by clyses. Under this management she gained 170 gm. (6 ounces) during the 1st 10 days in the hospital.

Gain in weight was not maintained, however, and her general clinical condition gradually deteriorated. Episodes of choking and gagging, with cyanosis and abdominal distention, became more pronounced. A 2d roentgenogram of the abdomen revealed generalized distention of the small and large bowel, without evidence of mechanical obstruction. On the 19th hospital day, exploration of the chest was decided upon, but before surgery could be undertaken, a particularly severe episode of respiratory distress necessitated an emergency tracheotomy. During this procedure

a catheter introduced into the opening of the tracheotomy tube passed readily into the stomach, confirming the clinical diagnosis of tracheoesophageal fistula. The child's condition was so precarious that further operative procedure was postponed. Two days after the tracheotomy, the temperature rose to 101.4°F., and respirations became labored and irregular. A roentgenogram of the chest showed a confluent pneumonic process or atelectasis, or both, in the right paracardiac region, with emphysematous changes in the remainder of the lungs. During the following night respiratory distress was severe. There was much thick, tenacious mucus in the oropharynx. Repeated suctioning and changing of the tracheotomy tube were without avail. The patient died on the 25th day of life.

At post-mortem examination, done within 12 hours of death, the esophagus was of a uniform diameter throughout its length, its circumference measuring 2.5 cm. (Fig. 1). On the anterior wall concentric folds of esophageal mucosa were seen hiding an opening, linear in shape, vertically placed and about 3 mm. long, which connected with the tracheal lumen (Fig. 2). The superior margin of the fistula lay 1.5 cm. below the inferior notch of the thyroid cartilage and about 2 or 3 mm. below the inferior margin of the tracheotomy wound on the anterior wall of the trachea (Fig 3).

The lungs, which were free from adhesions, were dark red. There were several areas of induration measuring up to 1.5 cm. in diameter. Normal crepitation was absent, generally. The findings were consistent with bilateral focal atelectasis and bronchopneumonia.

FIGURE 2. *Enlarged View of the Area Outlined in Figure 1. Note the concentric folds of esophageal mucosa overlying the opening of the fistula.*

The heart showed a small defect of the ventricular septum and a large patent ductus arteriosus; the pericardial cavity contained 5 to 10 cc. of clear, straw-colored fluid. The cecum, with a normal-appearing appendix, was lying near the midline of the body, and was very mobile. About half the small bowel was to the right of the ascending colon, which was fixed at the hepatic flexure, with the proximal two thirds attached to the posterior abdominal wall by a long, mobile mesentery. The intestinal mucosa was normal. The findings were consistent with partial malrotation of the ascending colon and cecum.

DISCUSSION

Haight,[6] Ladd and Swenson[2] and others[12] have described the various congenital anomalies of the esophagus. Over 90 per cent of all esophageal malformations consist of an atresia of the esophagus with the lower segment of the esophagus communicating with the trachea. The rarest anomaly, of which the case reported above is an example, is that of a tracheoesophageal fistula without esophageal atresia.

FIGURE 3. *Anterior View of the Posterior Tracheal Wall, Showing the Opening of the Fistula.*
The anterior portion of the tracheal rings has been removed. Arrows indicate the margins of the tracheotomy wound.

Unquestionably, the diagnosis of the anomaly may be difficult. The most important single factor contributing to this difficulty is the apparent rarity with which the condition occurs and the resulting unfamiliarity with it among physicians. It is the persistent demand for corroborative laboratory evidence, in the face of highly suggestive clinical findings, that

delays early diagnosis. That laboratory examinations are by no means infallible is generally agreed.

Three outstanding clinical features of tracheoesophageal fistula without esophageal atresia have been described[3]: the precipitation of paroxysms of coughing on feeding; gaseous distention of the gastrointestinal tract; and persistent pneumonitis. Haight[6] pointed out that the severity of paroxysms of coughing varies inversely with the viscosity of the feedings; liquids are much worse offenders than solids. The patient described above was fed only by gavage throughout the hospital course, but on occasion, after regurgitation of gastric contents, bouts of coughing and cyanosis did occur. Abdominal distention has been attributed to closure of the glottis on coughing or gagging and to the forcing of air from the trachea into the stomach through the fistulous opening. This distention may contribute to the respiratory distress. Sieber and Girdany[13] pass a tube into the stomach and observe the continued filling of the stomach with air under pressure when the infant cries or inspires vigorously; they have found this procedure useful diagnostically. In the infant described above, abdominal distention occurred in the supine position and tended to disappear in the prone position. The explanation for this phenomenon is not clear. It is well known that in infants, eructation of air from the stomach is facilitated in the prone position. In addition, one may speculate that, in the prone position, the fistulous communication somehow became sealed off by the concentric fold of the esophageal mucosa around the opening, preventing the passage of gas from the trachea into the esophagus and stomach and thus also accounting for failure to visualize the fistula radiographically in the prone position. The pneumonitis is caused by the aspiration of esophageal contents and is said to involve the right upper lobe most often; in the case reported above, both upper-lung fields were involved. An increased amount of mucus in the mouth, nose and throat is also characteristic of this condition. This mucus often has a frothy appearance and may be the presenting symptom, as it was in this case.

Bronchoscopic and esophagoscopic examination are important diagnostic aids. Imperatori[14] reports the finding of a fistula with the bronchoscope. Abbott[15] also employed bronchoscopy to visualize the appearance of a dye (methylene blue) in the trachea after its instillation into the esophagus. Esophagoscopy was employed by Clerf[16] in 1 patient to locate the fistulous opening in the esophagus. Endoscopy is probably the most exact method of determining the level of the fistula and should be performed in every case in which the location is doubtful.[3]

In the case reported above, the diagnosis was not confirmed until a catheter was passed from the trachea into the stomach during tracheotomy (Fig. 2).

The most helpful laboratory method in diagnosis is radiographic demonstration of the fistulous communication between the trachea and the esophagus, which one can do by outlining, during fluoroscopy, the fistula with the aid of radiopaque contrast mediums. Iodized preparations, such as Lipiodol and Diodrast, are the agents of choice. Barium is not to be used. The medium is instilled in the esophagus through a catheter. Whereas most authors insist that the examination be done with the patient in the prone position, to allow the medium to enter the trachea by gravitation, others[17] take the view that in this position the opacified esophagus hides the tract and the trachea; they recommend the anterior oblique position. In cases in which this technic does not demonstrate the fistula, Leigh et al.[17] recommend the use of tracheograms, because the rigid tracheal wall is less likely than the flaccid esophagus to collapse around the opening. The use of Diodrast is recommended by Cardullo and Berens[10] because of its low viscosity, which permits readier passage through a small fistulous communication.

It is important to bear in mind that failure to visualize the fistula does not exclude its presence. When highly suggestive symptoms persist, examinations should be repeated. If these efforts prove fruitless, surgical exploration must be seriously considered.

Summary and Conclusions

A case of congenital tracheoesophageal fistula without esophageal atresia in a newborn infant is described along with the post-mortem findings. A brief discussion of difficulties in diagnosis and a review of helpful laboratory examinations are included.

This diagnosis should be considered in all infants with large amounts of mucus in the pharynx and mouth associated with frequent coughing, abdominal distention and a persistent pneumonitis. Early diagnosis and surgical intervention are imperative.

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SPECIAL ARTICLE

A BRIEF HISTORY OF THE MASSACHUSETTS MEMORIAL HOSPITALS (1855 - 1955)

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THE history of an institution can never be more than the story of the people whose dedicated effort, loyalty and devotion give to bricks and mortar the intangible characteristics that create a personality. This account of the Massachusetts Memorial Hospitals during its first hundred years deals more with people and their achievements than with structural development because through them the character of the institution has emerged. Emphasis on their goals and accomplishments should aid in the rededication of another century to the all-important task of health service—a rededication that will involve continuing care of the sick, intensified effort to increase the body of scientific knowledge through research and broadening the opportunities for education in the health professions.

FOUNDING AND EARLY DEVELOPMENT

It was on May 19, 1855, that Governor Henry J. Gardner signed an act incorporating the Massachusetts Homeopathic Hospital. The eleven prominent citizens mentioned in the Act of Incorporation included Otis Clapp, founder of a pharmaceutical firm; John Punchard Jewett, the publisher of *Uncle Tom's Cabin;* and Jacob Sleeper, an eminently successful businessman and philanthropist. William Claflin, former governor of Massachusetts, and Drs. Conrad and William P. Wesselhoeft were early members of the hospital corporation.

The founders and physicians associated with the early history of the hospital were a vigorous group of determined individuals inclined to favor homeopathy, which had been introduced in America in 1825 by Dr. Hans Burch Gram, a Boston-born physician who received his medical education in Denmark. Although homeopathy became a popular vogue, a committee of the Massachusetts Medical Society issued a statement in 1850 that "commended the Society to do no more than avoid giving positive sanction" to this unorthodox theory.

Because of insufficient funds, the establishment of the hospital was delayed. In 1856, however, John H. Wilkins, Charles B. Hall and Jacob Sleeper, among others, were named as incorporators of the Massachusetts Homeopathic Medical Dispensary. This institution, located in one room in Tremont Temple at Washington and Boylston Streets, was opened to the public in 1857. In 1871, the Dispensary was moved to a small house at 14 Burroughs Place, just behind the present Metropolitan Theatre. A College Dispensary Branch was established in the Boston University School of Medicine building on East Concord Street in 1873. A West End Branch of the Dispensary was opened on Leverett Street in 1876. In the following year this was moved to 28 Causeway Street and finally was located in the Charity Building on Chardon Street. The rules and regulations state:

> Patients too sick to come to the Dispensary for treatment may be attended in their homes. The attending physician may authorize medical students in their senior year of study to visit them under his supervision. He shall require to be made to him, from day to day, a careful report of all such cases and shall give directions as to their treatment.

A supporting statement in the third annual announcement of the Boston University School of Medicine in May, 1875, notes that "advanced students are allowed to visit patients in their homes and treat them under the direction of attending physicians."

In 1869, Dr. F. H. Krebs called to the attention of the Massachusetts Homeopathic Medical Society the fact that it held charters for the establishment of a medical school and hospital. In the following year, a committee of ten, consisting of Drs. David Thayer, W. P. Wesselhoeft, Conrad Wesselhoeft, G. N. Pease, Charles Cullis, I. T. Talbot, D. G. Woodbine, H. C. Angell, E. B. de Gersdorf and J. H. Woodbury, recommended the establishment of a hospital. This was established in 1871 with 16 beds in the upper floors of the building at 14 Burroughs Place, the basement of which was occupied by the Dispensary. It was Dr. Israel Tisdale Talbot who co-ordinated the scattered forces of homeopathy and converted them into a united body of harmonious and successful activity. The hospital probably owes more to his influence than to that of any other person.

At this time, a minority of the Massachusetts Medi-

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cal Society developed an attitude of extreme bitterness toward homeopathy that culminated in the notorious trial of 1871-1873. A record of the proceedings is preserved in a volume of famous Massachusetts trials in the Boston Athenaeum. Among the accused were Dr. I. Tisdale Talbot, surgeon-in-chief of the Massachusetts Homeopathic Hospital, and Dr. David Thayer, an incorporator and staff member.

The principle of homeopathy, however, continued to be popular, and under the leadership of Drs. Talbot, Thayer, Wesselhoeft and others, the task of raising funds for a new building was undertaken. The Ladies' Aid Association conducted "one of the most brilliant Fairs ever held in Boston," at which $76,000 was realized for this purpose. A land site was purchased on East Concord Street between Harrison Avenue and Albany Street adjoining the Boston University School of Medicine. The change from the temporary hospital on Burroughs Place to the new spacious building on East Concord Street (Fig. 1) in 1876 was hardly more agreeable to the patients than to the members of the staff.

FIGURE 1. *Massachusetts Homeopathic Hospital (Right) and Boston University School of Medicine (Left) in 1876.*

Despite the availability of a new 40-bed building, all operations were performed in the anatomic amphitheater of the Boston University School of Medicine on Saturdays until 1884, when a surgical wing was added to the original building. This construction, in addition to a cottage ward for contagious diseases, was undertaken on land conveyed to the hospital by the City of Boston and raised the bed capacity to 73.

In 1885, the School of Nursing, one of the early schools of nursing in New England, was founded. Four students graduated in 1887, the same year that electric lights were installed in the hospital. In the ensuing years, the need for expansion resulted in the establishment of a medical wing and a surgical annex in 1892, bringing the bed capacity up to 225. This was made possible by a grant of $120,000 from the Commonwealth of Massachusetts, which was approved by the Legislature on June 3, 1890. A maternity department at 40 West Newton Street followed in 1897.

It is quite apparent in reviewing the early history of the hospital that significant and essential contributions were made by a loyal and spirited group of women. Even before the election of the first board of trustees of the hospital, a group of interested women raised funds to aid in furnishing the hospital. The principals behind this effort all bore familiar names: Mrs. I. T. Talbot, Mrs. E. B. de Gersdorff, Mrs. J. H. Woodbury, Mrs. H. C. Angell and Mrs. C. Wesselhoeft. On December 14, 1870, they formally organized the Ladies' Aid Association. Time and again through the years, the Board of Trustees and the Medical Board have voiced their appreciation to the members of this Association "for their liberal, timely, and persevering assistance which has contributed in many ways to the comfort and recovery of patients." With some justification, perhaps, the good ladies thought that their sex should be represented on the Medical Staff. There was no evidence of restraint or hesitancy in their request to the trustees. In fact, the name of their candidate was clearly mentioned in their recommendation, and Dr. Mary Safford Blake was duly appointed to the Medical Staff in 1875.

The properties, assets and liabilities of the New England Female College were assumed by Boston University in 1873, and a new Medical School was established. The relation to the Massachusetts Home-

opathic Hospital is fully appreciated when it is realized that Dr. Israel Tisdale Talbot was named dean and professor of surgery. Dr. John H. Woodbury was registrar and professor of diseases of women. Dr. Conrad Wesselhoeft was professor of materia medica and therapeutics. Dr. David Thayer was professor of the practice of medicine, and Dr. E. B. de Gersdorff was professor of pathology. Dr. F. H. Krebs was professor of obstetrics, and Dr. Walter Wesselhoeft professor of anatomy.

Dr. Talbot was noted for his indomitable courage, determined character, executive ability and resourcefulness. Recently, in the *New England Journal of Medicine,* Dr. Henry R. Viets, in an article on "Mountaineering Physicians," noted that Dr. Talbot had climbed Mont Blanc in 1854. He was the second American to make the complete ascent. In 1853, he had climbed Mount Washington and in the following year, on August 25-26, he left on the peak of Mont Blanc a pebble carried from the top of Mount Washington. It is, perhaps, an interesting commentary that today, more than a hundred years later, people arrive quite breathless in the administrative offices of the Outpatient Department, located on the third floor of a building named in the memory of so peerless a mountain climber.

By 1897, it was the opinion of the Board of Trustees that the expansion of the Hospitals' activities required a change in administrative structure. It is not surprising that Dr. Talbot was the unanimous choice for the position of director of the hospital, a position that he held until his death in July, 1899.

In passing, it is of interest to note, in the report of the Medical Board for the year 1897, the recognition of the need for the application of scientific principles in the evaluation of the efficacy of homeopathic therapeutics. The impact of advances in medical sciences is readily apparent in the attitude of the staff. This, in reality, marked the beginning of a soul-searching inquiry. By 1900, the Medical Board recognized that there were some limitations to the use of homeopathic medication and emphasized the fact that it was important not to lose sight of advances made in the whole field of medicine.

Dr. William O. Mann succeeded Dr. Talbot as director of the hospital in November, 1899. For fifteen fruitful and progressive years, he conducted its affairs with ceaseless and tireless energy. It was during his administration that the hospital and dispensary were finally brought together into a single organization. The Homeopathic Medical Dispensary had continued to function at 14 Burroughs Place until 1891, when it moved to a new building erected on the corner of Harrison Avenue and Stoughton Street. In 1906, after forty-nine years of service to the community, the dispensary transferred all its property to the Massachusetts Homeopathic Hospital and became the Outpatient Department of the hospital.

The Memorial Buildings

The Massachusetts Memorial Hospitals is a group of five memorial buildings dedicated to the memory of persons particularly concerned with the growth and development of the institution.

Anna White Vose Hall

The first of the memorial buildings was provided for by a bequest made by Mrs. Anna White Vose in 1896. A permanent nurses' home with accommodations for 100 nurses in a building dedicated to the memory of the donor was completed on Stoughton Street adjacent to what was the new dispensary building in 1898. It was at this time that the course in the Training School was lengthened to three years.

FIGURE 2. *Haynes Memorial Department of Infectious Diseases.*

John C. Haynes Memorial

Early in 1907, Mr. John C. Haynes, then a vice-president of the hospital, made a most generous offer to erect a building for the care of contagious disease. The building (Fig. 2), which was built for 100 patients and was located on Corey Hill in Allston, was completed and turned over to the hospital on September 30, 1908. The total cost was nearly $300,000. The first patient was admitted on October 22, 1908. Two months later, there were in this new unit 40 patients with diphtheria, and 82 patients with scarlet fever.

Of particular interest is the fact that before the building was opened the trustees voted that any physician in good standing in the community would be permitted to treat his private patients in this unit. This action received favorable comment throughout the community.

Robert Dawson Evans Memorial

The most notable event of 1910 was the munificent gift, by Mrs. Marie Antoinette Evans, of a building

in honor of her husband to be called the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine. The building (Fig. 3) was erected on East Concord Street on land transferred to the hospital by Boston University. As time passed, Mrs. Evans added considerable sums of money to the endowment, and during her lifetime took a keen interest in its activities. It was the fundamental purpose of the donor to found an institution where the investigation of the cause, prevention and treatment of disease might be carried out. Dr. Frank C. Richardson, a personal friend of and physician to the Evans family, was appointed the first medical director by the trustees of the hospital.

FIGURE 3. *Main Hospital, with the Collamore Memorial in the Center, the Evans Memorial on the Left and the Robinson Memorial on the Right.*

Jennie M. Robinson Memorial

By 1911, the work of the Maternity Department had increased to such an extent that adequate space and facilities were no longer available. The trustees therefore proposed the erection of a maternity building above the one story of the Outpatient building on the corner of Harrison Avenue and Stoughton Street. Largely through a generous gift of Mr. Wallace Fullam Robinson, the Jennie M. Robinson Memorial (Fig. 3) for maternity and outpatients was completed in 1915 and dedicated on January 1, 1916.

Helen Collamore Memorial

On April 17, 1915, the Trustees learned of the death of a valued colleague. Miss Helen Collamore had been a trustee for thirty-eight years, and no member of the Hospital Committee had a more intimate knowledge of the affairs of the hospital. In her will she provided funds for a new building and made the hospital one of her residuary legatees. It was not until April 1, 1936, however, that the new building (Fig. 3), intended primarily for surgical patients, was completed and occupied. Dr. Howard M. Clute was the first surgeon-in-chief to make use of these new and modern facilities.

Israel Tisdale Talbot Memorial

As the history of the hospital is reviewed, one cannot but be impressed by the significant contribution to its growth and development made by Dr. Talbot. With widespread interests and a broad point of view, he brought to the medical school as its dean and to the hospital as its first director a significant degree of stature and presence. It was with the full appreciation of his importance that the trustees commemorated their appreciation of his efforts by naming the original hospital building the Israel Tisdale Talbot Memorial. This building, which once housed all the hospital's activities, was destined to become the present Outpatient Department.

A New Century

With the identification of the various memorial buildings that were to make up the hospital, it may be well to return to the events that transpired in the early part of the twentieth century. Dr. Conrad Wesselhoeft, a member of the Medical Board for more than thirty years and one of the vice-presidents of the hospital, died in 1904. He was a man of the highest professional attainments, recognized not only in this community but in medical circles all over the country and abroad. Both he and Dr. Talbot lived to see the remarkable development that followed the establishment of the original institution.

Under the direction of Dr. W. H. Watters, the Pathology Laboratory provided exhibits in various parts of the country. Special presentations for the Louisiana Purchase Exposition in St. Louis, the Lewis and Clark Exposition and others were prepared. At the exposition in St. Louis, the Laboratory participated in an exhibit on tuberculosis, for which it was awarded a gold medal. In 1908, the Pathology Department prepared another exhibit on tuberculosis for the International Congress on Tuberculosis and was awarded the silver medal for excellence. This collection was subsequently exhibited in New York City and was viewed by fully 800,000 visitors.

The Social Service Department was instituted in 1909 with one of the graduates of the School of Nursing in charge. In 1914, a trained social worker was appointed. Dr. Henry M. Pollock, who succeeded Dr. Mann as superintendent of the hospital in 1915, made an interesting comment on the function of this department:

> A hospital that devotes its efforts solely to the healing of the sick is but half performing its mission. The investigation of the underlying factors that were associated with the disease, and, when possible, their amelioration and the seeing that treatment is not abandoned before cure

is effected, and that the hospital is not involved in renewed expense by former patients returning to an environment or occupation that will tend to promote a recurrence of their trouble, is of equal importance.

As World War I approached, personnel of the hospital joined to form United States Army Base Hospital No. 44. With 32 medical officers, 100 nurses and 200 enlisted personnel, the Unit was assigned to duty in France. At Pouges-les-Eaux, with Lieutenant Colonel William F. Wesselhoeft in command, this unit, originally organized for a 500-bed hospital and later changed to 1000 beds, finally ended with a 1750-bed hospital.

Throughout the first seventy-five years of the hospital history, the trustees were almost continuously in the position of a parent trying to keep a rapidly growing boy adequately clothed. As soon as space, facilities and equipment were provided, they became overtaxed. In this fashion, the hospital grew by leaps and bounds from a small 16-bed institution to a modern hospital of more than 500 beds housed in a collection of memorial buildings. For more than half a century during which its doors had remained continuously open to the public, a throng of 187,347 men, women, and children entered to receive medical or surgical treatment. These patients came from every walk of life. All patients were accorded the same welcome, and at the disposal of each were placed all the facilities that the hospital afforded. Indeed, the sole determinants for admission were always a vacant bed and the possibility that benefit would accrue to the patient.

The Massachusetts Memorial Hospitals

For some time it had been considered that the hospital's name was restrictive and failed to convey its activities and liberal policies. In 1929, therefore, it was voted that the name be changed to the Massachusetts Memorial Hospitals to indicate the group of memorial buildings that comprise the institution. Although the name was certainly appropriate, its use introduced an interesting grammatical problem for those who attempt to apply a pluralized name to a single institution.

The hospital suffered a great loss through the death of Dr. J. Emmons Briggs, for many years chief of surgery at the hospital and professor of surgery at the Boston University School of Medicine. A progressive and able person, he had contributed much to the progress of both institutions. He was succeeded in 1932 by Dr. Charles T. Howard, who was in turn followed by Dr. Ralph C. Wiggin in 1934. A few months before the opening of the Collamore Memorial, Dr. Howard M. Clute was appointed surgeon-in-chief and professor of surgery. At the same time, Dr. Reginald H. Fitz was appointed director of the Evans Memorial to succeed Dr. Allan Winter Rowe, who died in that year. Dr. Edward S. Calderwood was physician-in-chief at this time. With superb leadership, the hospital began to emerge from the black days of the depression and to look to new construction to meet the increased needs of the Evans Memorial.

Dr. Chester Scott Keefer (Fig. 4) became director of the Evans Memorial for Clinical Research and Preventive Medicine as well as physician-in-chief in September, 1939. He brought to the institution an impressive ability as a teacher, a remarkable record as a clinical investigator and an inborn organizational skill. Under his supervision, reorganization and progress continued. A new Evans building at 65 East Newton Street was opened formally on Hospital Day, May 12, 1942. The old Evans Memorial building was transferred to Boston University School of Medicine and housed the administrative offices, library and several preclinical departments of the school.

FIGURE 4. *Ward Rounds with Dr. Keefer.*

The supervision of professional work at the Haynes Memorial continued under the admirable leadership of Dr. Conrad Wesselhoeft until 1947, when he retired. Dr. Wesselhoeft was a battalion surgeon in the 8th Massachusetts Infantry in service on the Mexican border in 1916. In World War I, he was awarded the Distinguished Service Cross for heroism in action near Verdun and the Oak Leaf Cluster for extraordinary heroism in action during the Aisne-Marne offensive. He was also awarded the Silver Star with Gold Leaf, the Purple Heart and the Croix de Guerre. He is now president of the Massachusetts Medical Society. His successor at the Haynes Memorial is Dr. Louis Weinstein, an able physician and productive investigator, who was a graduate of the Boston University School of Medicine. Under his direction, the Haynes Memorial has continued to be a recognized center for clinical research, education and treatment in the field of infectious disease.

The Evans Memorial developed swiftly in size and productivity. Cardiovascular research, with emphasis on hypertension and peripheral vascular disease, flourished under the able direction of Dr. Robert W.

Wilkins. Dr. Henry Lemon began studies on cancer. Dr. Joseph F. Ross, awarded the Certificate of Merit by the President of the United States for his contribution to the subject of blood preservation, carried on intensive studies in hematology and radioactive substances. Dr. Francis C. Lowell developed objective methods for the study of asthma, and Dr. Franz J. Ingelfinger explored the various aspects of the complex field of gastrointestinal diseases. Dr. Charles P. Emerson carried on studies in blood preservation. Without the development of this information, together with that from other laboratories, it would have been impossible for the United States Air Force to deliver whole blood collected in this country to the fighting forces in Korea. Dr. Emerson also worked out a rapid and simple technic for blood typing with easily available, inexpensive and disposable materials. This brief review serves but to skim the surface of the contributions in medicine made possible by the munificent gift of Mrs. Evans forty-five years previously.

While supervising these important activities at the Evans, Dr. Keefer participated in clinical investigations and served in many important capacities during World War II; the most important, perhaps, was his appointment as medical administrative officer, Committee on Medical Research, Office of Scientific Research and Development. He administered the program of distribution of penicillin so that information concerning its use could be collected promptly and passed on to the armed forces and civilians for the prevention and treatment of infections. He was awarded the Medal of Merit by the President of the United States and His Majesty's Medal for Services in the Cause of Freedom by Great Britain. With the establishment of the Department of Health, Education and Welfare, he was appointed special assistant for health and medical affairs by President Eisenhower. When the problem of the distribution of vaccine for poliomyelitis was undertaken on a national scale, he was appointed a special advisor to President Eisenhower.

Smithwick Foundation

Dr. Howard M. Clute found it necessary to resign as chief of surgery in 1945, because of poor health. His successor is Dr. Reginald H. Smithwick, internationally recognized for his studies on the neurosurgical approach to the problem of hypertension.

In 1946, the trustees of the hospital approved the establishment of the Smithwick Foundation. The purpose of this development was to further the advancement of surgery through patient care, research and teaching. It was the hope of the surgeon-in-chief that the Foundation would, in time, be able to subsidize the activities of a number of full-time members of the surgical staff. The Foundation did, in fact, begin the organization of a geographically full-time nucleus of surgeons within the Department of Surgery and gave support to research, teaching and patient care. The success of the Foundation indicated that a larger group organized in a similar fashion should be even more successful in attaining the same objectives on a broader base.

In 1948, a most noteworthy event involved the Surgical Services — namely, the creation of a new division of obstetrics and gynecology, with Dr. Benjamin Tenney, Jr., as the head of the new division. Dr. Tenney continued in this position until 1953, when he assumed the position of director of teaching in obstetrics at the Boston City Hospital. He is succeeded by Dr. Langdon Parsons as head of the Division of Obstetrics and Gynecology.

Medical Associates

The organization of the Medical Associates was preceded by the realization that further development of the group approach to the complex problem of medical care was needed. The nucleus of physicians who pioneered the organization of this particular group either were members of or were very familiar with the development and progress of the Smithwick Foundation. The Foundation thus served as a natural stepping stone for the development of the Medical Associates of the Massachusetts Memorial Hospitals, which was established as a new and separate division of the hospital and had its formal beginning on March 1, 1951.

Although most of the participating members of the Associates maintained private practices, an increasing number of group services were developed that included periodic examination of executive personnel, the management of dispensary services for industrial groups, and contractual arrangements for varied services with a number of organizations.

New Developments

As the history of the Massachusetts Memorial Hospitals is reviewed, there are many instances that reflect a broad understanding of health needs in terms of practical program development. One such occasion was the public announcement in April, 1955, of the establishment of a unit, under the direction of Dr. Donald Munro, at the Haynes Memorial to deal with one of the most difficult and complex human problems, the rehabilitation of the paraplegic patient.

Care of the patient in his home, which was provided by the Homeopathic Medical Dispensary, continued uninterruptedly through the years. In 1955, the Home Medical Service was established as a separate service within the Division of Medicine, with Dr. Henry J. Bakst as chief. Domiciliary medical care was extended to 6500 patients annually, 18,000 home visits being made within a square-mile area surrounding the hospital and medical school. This area is populated by approximately 50,000 residents, for the most part from a low-income, multi-racial stratum of society. Students on the service include

not only those from the medical school but also students from the Boston University School of Social Work and third-year students from the Massachusetts Memorial Hospitals School of Nursing, as well as students from the Andover-Newton Theological Seminary. Thus was developed a true teamwork approach to the provision of medical care.

Dr. William Malamud was appointed professor of psychiatry and chief of the Psychiatric Service of the Hospitals in 1946. Under Dr. Malamud's direction, this department made a spectacular development and was soon recognized as one of the leaders in this field. Well merited recognition was given to this department in 1954 by the award of the first United States Public Health Service Career Investigatorship to Dr. Peter Knapp, assistant visiting physician in psychiatry. Emphasis in psychiatry at the Massachusetts Memorial Hospitals is on the prevention of major mental illness, mental hygiene for children, study of emotional factors in organic illness and research in the prevention and control of seizures. In 1955, this department was established as a separate division in the hospital with Dr. Malamud as psychiatrist-in-chief and joined with medicine, surgery and obstetrics and gynecology to become one of the four main clinical divisions of the hospital.

It is unfortunate that the limitations of space do not permit mention of all of the devoted members of the hospital family who have contributed to its progress and development. Today, with the perceptive and sensitive administration of Dr. Philip D. Bonnet and the able and understanding leadership of Mr. Jerome Preston, supported by a board of trustees instilled with the traditions of the past, the hospital looks forward to the discharge of its responsibilities in a manner that will continue to deserve the trust, admiration and respect of the community that it serves.

Conclusions

The history of the Massachusetts Memorial Hospitals reveals an unflagging concern with the problems of health education and medical care. Many changes took place in the first century of the hospital's existence. It is interesting, in looking backward, to relate these changes to processes that had been going on in the country as a whole.

Today, as the hospital stands on the brink of a new century, new roads to health have opened and new problems are recognized. Since services, facilities and equipment once established and proved tend to become relatively fixed, it is essential, in recognizing the health needs of today, to attempt a reasonable prediction of the requirements of tomorrow. Looking backward with the support of experience and historical perspective is a relatively simple task. Looking ahead in a complex and intricate world to which new knowledge is introduced at an extraordinarily rapid pace is a difficult and treacherous occupation.

With courage, determination and united effort, however, the Massachusetts Memorial Hospitals now dedicates itself to another century of service and progress.

MEDICAL PROGRESS

METABOLISM AND CLINICAL SIGNIFICANCE OF THE CARBOHYDRATE COMPONENTS OF CONNECTIVE TISSUE*

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CARBOHYDRATE is necessary in the body, not only as a source of energy but also as an integral part of its structure and functional components, connective-tissue matrix, nucleic acids, galactolipids of brain and many proteins. The serum, for instance, contains more hexose as part of macromolecules than in the free state, and almost as much hexosamine. Changes in the concentration of these substances occur in a wide variety of diseases. A carbohydrate, hyaluronic acid, is the chief component of synovial-fluid mucin, which usually deteriorates in active rheumatoid arthritis, providing an important clue to the diagnosis of this disease. Hexosamine-containing compounds are present in relatively large quantities in the retro-orbital tissues of patients with malignant exophthalmos, and in amyloid (as pointed out below). Because of the importance of the structural carbohydrates in the body, and the possibility that faulty metabolism of these compounds is involved in the pathogenesis of a number of diseases, it seemed appropriate to compile a brief summary of present knowledge in this rapidly expanding field.

Since a great deal of confusion exists at present because of conflicting nomenclature, a classification of these components is first reviewed.

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Classification and Chemistry

Although hexoses and hexosamines, as monomers, undoubtedly occur in the bound state, the most characteristic structural carbohydrates occur in polymeric form. The best defined of these compounds are the mucopolysaccharides. In contrast to glycogen, starch, dextrans and inulin, so-called "homopolysaccharides," in which each monomer is identical with the next, the mucopolysaccharides appear to comprise two or more compounds, one of which is an

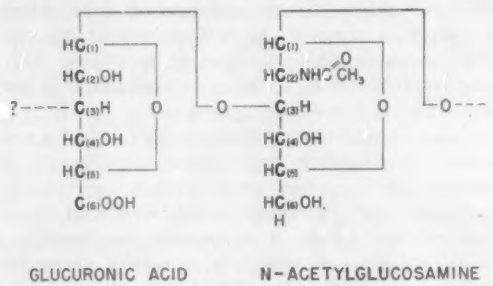

Figure 1. *Chemical Composition of the Basic Disaccharide Unit of Hyaluronic Acid.*
The exact site of the bond indicated by the dotted line is not certain.

amino sugar. Probably the best known of these mucopolysaccharides is hyaluronic acid, composed of D-glucuronic acid and N-acetyl-D-glucosamine. As shown in Figure 1, N-acetyl glucosamine differs from glucose in having an NH_2 group on C_2 instead of a hydroxyl group, and glucuronic acid differs from glucose in having a COOH group on position 6. The acetyl group is known to be attached to the amine group, and the linkage between glucuronic acid and N-acetyl glucosamine is known to be in the 1,3 position as shown in Figure 1.[1,2] On the other hand, the site of attachment between the N-acetyl-glucosamine and the succeeding glucuronic acid molecule is not certain. Hyaluronic acid and other mucopolysaccharides usually exist in loose association with a protein. The precise nature of this association is not well understood. Nevertheless, in contrast to the mucoproteins, it is possible to separate the components of a protein-mucopolysaccharide complex without destroying the polysaccharide. A more detailed discussion of the chemistry of hyaluronic acid has recently been presented by Jeanloz.[3]

The chemical components of several of the other mucopolysaccharides are listed in Table 1 and are discussed below. In addition there are in the body a number of other acid-containing polysaccharides — for example, those tentatively classified under the names mucoitin sulfuric acid,[4] dermatoidin sulfuric acid[5,6] and so forth. Nevertheless, there has as yet been no general agreement concerning either the nature of these compounds or their composition. In addition, recent studies have shown that various connective tissues contain carbohydrate fractions that are free of uronic acid. One such compound is keratosulfate, which has been found in beef cornea.[7] Furthermore, carbohydrates containing neither uronic acid nor hexosamine have been found in a number of tissues. They are composed chiefly of galactose, glucose and mannose, together with some fucose.[8,9] Their nature and importance are undefined.

Mucoproteins are predominantly protein and yet contain a significant amount of tightly bound carbohydrate. Although Meyer[10] has proposed the term "glycoprotein" for a mucoprotein containing less than 4 per cent hexosamine the distinction is somewhat arbitrary and is not adhered to in this report.

Intermediate between the mucopolysaccharides and the mucoproteins are the blood-group substances. Studies of extracts exhibiting blood-group activity have shown that this activity is displayed by fractions containing amino sugars and sugars, tightly bound to amino acids.[11] It is probable that in nature these amino acids exist as part of larger polypeptides or possibly as proteins.[12]

Hexosamines and uronic acids exist in the plant and animal kingdom as homopolysaccharides as well as heteropolysaccharides. Thus, chitin, the chief component of arthropod skin and of the exoskeletons of crustacea and certain fungi, is a polyacetylglucosamine, and pectic acid, occurring in many plants, is a polyuronic acid.[13]

Table 1. *Components and Distribution of Mucopolysaccharides Best Characterized at Present.*

Compound	Composition	Distribution
Hyaluronic acid	N-acetyl-D-glucosamine D-glucuronic acid	Synovial fluid; vitreous; umbilical cord; skin; bone.
Chondroitin sulfuric acid	N-acetyl-D-galactosamine D-glucuronic acid sulfate	Cartilage; aorta; tendons.
Alpha-heparin	D-glucosamine D-glucuronic acid sulfate	Mast cells
Beta-heparin	N-acetyl-D-galactosamine D-glucuronic acid (?) sulfate	Mast cells (?)
Keratosulfate	N-acetyl-D-glucosamine Galactose sulfate	Cornea

Distribution and Function

Hyaluronic Acid

First isolated in its pure form in 1934 from vitreous humor by Meyer and Palmer,[14] hyaluronic acid has subsequently been shown to be a major component of synovial fluid as well.[15,16] It has also been found in fairly high concentration in the umbilical

cord and skin. The fact that these tissues contain a large amount of amorphous matrix or ground substance has led to the extrapolation that hyaluronic acid is one of the components of this substance. Although hyaluronic acid has recently been found in heart valves[17] it has not yet been isolated from tendon, aorta and hyaline cartilage, other chief sites of chondroitin sulfate.

The mode of synthesis of hyaluronic acid in synovial fluid is not fully understood. Nevertheless, it is believed that it bears the same relation to the mesodermal cells surrounding the synovial cavity that hyaluronic acid in ground substance bears to the fibroblasts.[18] The "mucin" of synovial fluid is thus of quite different origin from the mucins of epithelial origin (salivary, tracheobronchial, gastric and so forth). The term "mucin" refers to the viscous material in synovial fluid, which precipitates under the influence of acetic acid and other substances to form a ropy, fibrous clot.[10] Synovial fluid contains both polysaccharides and proteins, and the "mucin" precipitate also contains both substances. The nature of the association between hyaluronic acid and protein in normal synovial fluid is not clear.[10,15,19,20] Although much of the viscosity of normal synovial fluid can be attributed to the long hyaluronic acid polymers, the degree to which this may be increased by the association with protein is not certain.

Sulfated Mucopolysaccharides

The sulfated mucopolysaccharides are found primarily in the supporting tissues of the body. Of this group of compounds, the *chondroitin sulfates* are the best known. They are the chief component of cartilage, and also occur in the walls of the large blood vessels and in tendons, heart valves and skin.[16,21] Although chondroitin sulfates are known to be composed of D-glucuronic acid, N-acetyl-D-galactosamine and sulfate, the exact structural formula is not certain. There is good evidence, based on optical rotation studies and differing enzymatic reactions, that chondroitin sulfate from skin is in some respects different from the chondroitin sulfate of cartilage.[22]

It seems probable that the chondroitin sulfates, being poly-acids, with large negative surface charge, have a marked cation-binding capacity. Recent studies support this view. One group of investigators[23] measured the binding of electrolytes by ground cartilage, packed in glass columns. They demonstrated that the binding was an ion-exchange reaction due primarily to the chondroitin sulfate present. Binding capacities for sodium, calcium and barium were equal. A second group[24] studied the electrochemical potential across various connective tissues and obtained evidence that the dense connective tissues, because of their great particle-charge density, bind calcium ions in a concentration many times that in serum. Detailed studies of the binding of cations by the cornea are soon to be reported.[25]

Heparin

The heparin group of compounds, especially alpha heparin, are even more highly charged than the chondroitin sulfates. They occur in highest concentration in mast cells..[26] They are also found in certain organs, notably liver capsule, lung and heart, presumably because of the mast cells therein. The anticoagulant property of heparin is thought to be a manifestation of the ability of this negatively charged colloid to enter into loose physicochemical combination with certain plasma proteins.[27] This property is not peculiar to heparin but is shared by other synthetically sulfated polysaccharides.

Another interesting property of heparin is its ability, on intravenous injection into animals and man, to reduce the turbidity of lipemic plasma. It has been shown that this is due to the activation by the polysaccharide of an enzyme in the plasma, lipoprotein lipase, which catalyzes the hydrolysis of the neutral fat chylomicrons.[28] Whether this property of heparin, or its anticoagulant effect, indicates physiologic roles for this compound or represents a pharmacologic curiosity is still not clear. The former possibility is supported in part by the fact that circulating heparin has been found in dogs during acute anaphylactic shock.[29]

Beta heparin, which is more difficult than alpha heparin to extract from tissues, is less active as an anticoagulant. It more nearly approaches chondroitin sulfuric acid in its chemistry.[30]

Mucoproteins

Mucoproteins perform a number of important physiologic roles, both specific and nonspecific. At least four gonadotrophic hormones are mucoproteins: pregnant mare's serum gonadotropin, human chorionic gonadotropin, follicle-stimulating hormone and interstitial-cell hormone. This is also true of thyroglobulin. Serum albumin and alpha, beta and gamma globulins also contain measurable amounts of carbohydrate. It is interesting to speculate concerning a possible physiologic significance of the carbohydrate portion of mucoproteins. Stacey[31] has suggested that this prosthetic group is somehow connected with the enzyme that synthesizes proteins. In this regard it is of interest that the preponderance of protein in a chicken egg is mucoprotein (ovomucoid) and that a mucoprotein (fetuin) is present in large amounts in the serum of fetal calves.[32]

Blood-Group Substances

The blood-group substances have achieved clinical importance by virtue of their location on the red-cell membrane and their antigenicity, thus necessitating blood typing and matching. They are also widely spread through the body, having been demonstrated in gastric mucin, saliva, urine and cyst fluids.[11] The substances from different tissues in a given person display the same antigenic specificity.

Mucins of Epithelial Origin

The mucins of epithelial origin are poorly characterized both chemically and functionally. Since they are not of mesenchymal origin they do not properly belong in this review. Nevertheless, two of their specific actions are known and might be mentioned briefly. A mucoprotein from gastric secretion has been shown to exhibit marked intrinsic-factor activity in pernicious anemia,[33] and raises the question, Could this substance represent Castle's intrinsic factor? Secondly, carbohydrate-containing substances in gastric secretion and sputum have been found experimentally to influence the action of certain bacteria and viruses.[34,35] Could compounds of this sort in the lung and bronchi participate in host resistance and susceptibility to respiratory infection?

Metabolism

It is evident from the summary presented above that the mucopolysaccharides and related compounds are common components of many tissues and biologically active substances. The metabolism of these components, in vivo, has not been extensively investigated. It seems fairly certain that the chondroblasts are responsible for the formation of chondroitin sulfuric acid in cartilage, and recent studies strongly suggest that hyaluronic acid is synthesized by fibroblasts.[36] The site of synthesis of heparin has not been definitely established, although histochemical evidence suggests that the mast cells are involved.[26]

Studies of the rate of metabolic exchange of the mucopolysaccharides in various tissues, with the use of S^{35} and C^{14}, have indicated that this exchange is active. Studies of the sulfated mucopolysaccharides have been carried out chiefly with S^{35}. In one report of a series of experiments the radioactivity of the ester sulfate of mucopolysaccharide from rat skin, separated electrophoretically, reached a maximum twenty hours after (intravenous) injection of S^{35}, and declined at a rate indicative of a half life of approximately ten days.[37] The uptake of S^{35}-labeled sulfate by cartilage slices has also been demonstrated after incubation in vitro both under basal conditions and under the influence of various steroids.[37,38]

Hyaluronic acid also has an active metabolic exchange. In one study of hyaluronic acid and sulfated mucopolysaccharide fractions obtained from rabbit skin, after administration to the animal of C^{14}-labeled acetate and glucose, the rate of incorporation of C^{14} in hyaluronic acid was approximately three times that into the sulfated mucopolysaccharide fraction.[39] Other studies showed that the rate of incorporation of C^{14}-labeled acetate by hyaluronate and chondroitin sulfate of skin was reduced to approximately a third in diabetic rats.[40]

Biosynthesis of Hyaluronic Acid in Vitro

Understanding of the process by which the body synthesizes a compound requires two steps: demonstration of the precursors and over-all pathways by isotopic technics, and elucidation of the enzymatic mechanisms involved in these conversions. The over-all pathways were clarified by the work of Roseman et al.,[41-44] who demonstrated, by isotopic technics, with intact Group A streptococci, that glucose was incorporated in the glucosamine and glucuronic acid of hyaluronic acid without scission of the glucose molecule and that glucosamine could be incorporated into the hyaluronic acid without previous deamination.

Knowledge of the enzymatic mechanisms involved in the formation of polysaccharides stems from the observations of Leloir and his associates.[45-48] In 1949 they obtained extracts of galactose-fermenting yeasts, *Saccharomyces fragilis,* which catalyzed the conversion of galactose-1-PO_4 to glucose-1-PO_4. In addition to a thermolabile enzyme "galacto-Waldenase," a thermostable factor or coenzyme was found to be necessary.[45] Analysis showed it to be uridine diphosphate glucose ("UDPG"). This substance was also found in yeast that did not ferment galactose, suggesting that it might possess some other action. In searching for other functions for this coenzyme they found that it was involved in the synthesis of disaccharides from monosaccharides, the glucose of the UDPG being transferred to the monosaccharide.[46-48]

Studies on partially purified preparations of this coenzyme, obtained from yeast, revealed the presence of an analogous compound, uridine diphosphate N-acetyl glucosamine.[49] Leloir and his associates[49] therefore wondered whether this compound might be involved in the metabolism of hexosamine phosphates and in its incorporation into mucopolysaccharides. To study this possibility, they centered their attention on a mold, *Neurospora crassa,* on the assumption that since molds have walls containing large amounts of chitin (a polyhexosamine) they must contain a mechanism for synthesizing this substance. They demonstrated that cell-free extracts, upon the addition of glutamine, could synthesize glucosamine-6-PO_4 from fructose-6-PO_4.[50,51] Uridine diphosphate acetylglucosamine was not necessary for this reaction.

In the meantime, other investigators had demonstrated that uridine diphosphate glucuronic acid was the donor for the glucuronide portion of phenyl glucuronide[52] and, more recently, that uridine diphosphate glucuronic acid is synthesized from uridine diphosphate glucose enzymatically in vitro.[53] This finding provided for the first time a probable explanation of the mechanism by which the body synthesizes glucuronic acid, which is important not only as a component of mucopolysaccharides but also in the "detoxification" of acetyl salicylic acid, chloramphenicol, morphine, thyroxine, many steroids and other substances.[54] Recent studies of Isselbacher and Axelrod[55] showed that uridine diphosphate glu-

curonic acid was the glucuronide donor in the in vitro synthesis of the glucuronide of tetrahydrocortisone and suggested that this might apply to other glucuronides as well.

The possibility that uridine diphosphate-N-acetylglucosamine is involved in the synthesis of polymers of N-acetyl hexosamine, such as chitin and hyaluronic acid, has been under investigation by several groups. Recently, evidence has been presented that this may indeed be so. Glazer and Brown,[56] using cell-free homogenates of Rous chicken sarcoma, demonstrated the synthesis of short-chain oligosaccha-

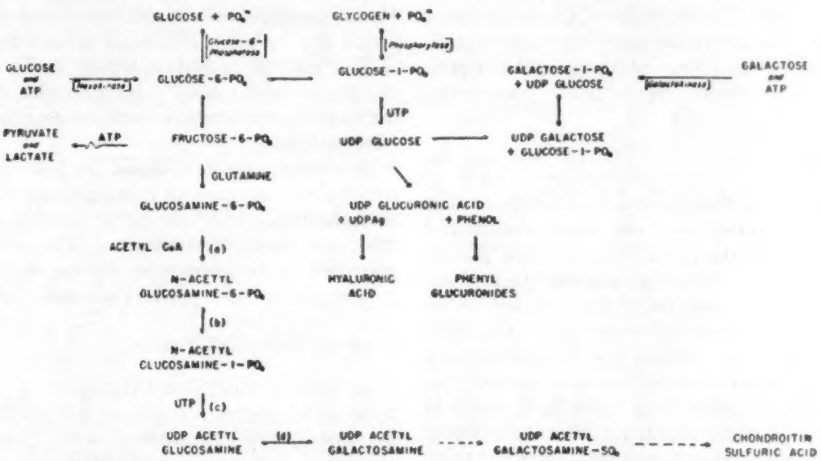

FIGURE 2. *Tentative Scheme for the Interconversion of the Body-Sugar Components Based on in Vitro Enzymatic Studies. The interrupted arrows are postulated reactions. Evidence for the steps designated by the letters* a, b, c *and* d *is available.*[50,57,58]

rides of the hyaluronic acid type after incubation with uridine diphosphate-N-acetylglucosamine, or its precursors, and precursors of uridine diphosphate glucuronic acid. By means of these and other studies it is possible to draw a tentative scheme for the mechanism of the interrelation between glucose and some of the carbohydrate intermediates (Fig. 2).

Demonstration of the importance of uridine diphosphate in the synthesis of substances containing hexoses and hexosamines has theoretical connotations beyond this individual system. This observation, together with the earlier documentation of the role of adenylic derivatives in catalytic processes, suggests the possibility that the other purine and pyrimidine bases found in nucleic acids will prove to be parts of coenzymes.[59] Indeed, of the known nucleic acid bases, all but 5-methyl cytosine and thymine have been demonstrated to be components of coenzymes.

Clinical Implications

Application of this growing bulk of information to human diseases has been slow to develop. As in many other areas of clinical investigation, studies on the composition of body fluids, especially the blood, have far outnumbered those of tissue.

The concentration of protein-bound carbohydrate has been determined in the serum of normal persons and in patients with various diseases. Different investigators use different methods. Some measure the total nonglucose serum carbohydrate (Seibert[60]), others the "nonglucosamine polysaccharide" (Shetlar[61]), the glucuronate containing polysaccharide (Schubert[62]), and the carbohydrate bound by proteins that are soluble in strong acids (Winzler[63] and Greenspan[64]), and still others simply the serum hexosamine (Boas[65]). There is considerable overlap among these various fractions, and their significance is not entirely understood. All these studies show the same trend — that the protein-bound carbohydrate content of the serum is significantly elevated in neoplastic diseases, rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, pregnancy, diabetes mellitus associated with vascular complications, tuberculosis, myocardial infarction, obstructive liver disease, irradiation and aging.[60-68] A decrease in at least one of these fractions in the serum of patients with diffuse parenchymal liver disease has been reported.[64] The elevated levels observed in patients with acute rheumatic fever and lupus erythematosus disseminatus fall to normal after clinically effective treatment with ACTH or cortisone.[65,69]

Some authors have suggested that the increased serum protein-bound carbohydrate level in inflammatory diseases of connective tissue and in the presence of tissue necrosis may reflect flooding of the extracellular fluids with the products of tissue breakdown. Conversely, it has been theorized that the increased serum hexosamine in diabetic patients with vascular complications may reflect an increased rate of synthesis of mucoproteins.[67]

Unfortunately, insufficient experimental work has been carried out in either human subjects or animals

to permit clear understanding of how the mucopolysaccharides and mucoproteins of the tissues are related to those of the serum. In one interesting series of animal experiments, however, Boas[70] has obtained evidence that the elevation of plasma hexosamine in response to the stress of surgery is hormonally mediated, presumably by the thyroid or pituitary gland. Although this response was not inhibited by adrenalectomy, it was inhibited by hypophysectomy or by thyroidectomy. This hypothesis was supported by the demonstration of a high serum hexosamine concentration in a patient with Addison's disease during high fever.[65] In addition to studies on the relatively nonspecific fractions discussed above, there have been a few observations on specific and fairly well characterized mucoproteins. One of these is the alpha$_1$ acid glycoprotein isolated by Schmid[71] from serum and synovial fluid.

Synovial Fluid

Although synovial fluid provided one of the earliest sources of hyaluronic acid, the exact nature and mode of genesis of the hyaluronic acid and protein complex ("mucin") in normal synovial fluid is still not understood, nor have the changes caused by inflammatory disease been fully explained. It is generally agreed that the synovial fluid in patients with rheumatoid or infectious arthritis has a reduced viscosity and that the addition of acetic acid results in the precipitation of an abnormally loose and shredded clot. Studies have shown that these changes cannot be accounted for on the basis of simple changes in concentration of hexosamine and protein.[15,72-74] It is likely that some qualitative change has taken place, presumably owing to alterations in the degree of polymerization of hyaluronic acid or, in addition, to alterations in the polysaccharide protein complex. Whether this abnormality represents excessively rapid breakdown of the long-chain molecule or faulty synthesis of hyaluronic acid is not known. Attempts to demonstrate hyaluronidase activity in the synovial fluids of normal persons or patients with rheumatic diseases have not been successful.[73]

Histochemical Studies of Tissues

Studies of abnormal connective tissues have relied almost entirely on histochemical technics, chiefly metachromasia on staining with toluidine blue. Increased metachromasia of the ground substance has been shown to occur in granulation tissue, wound healing, rapidly growing tissues such as embryos and neoplasms, accumulations of fibrinoid in rheumatoid arthritis and other diseases, the hearts of patients with myocarditis due to rheumatic fever or lupus erythematosus disseminatus, amyloid deposits, at sites of normal and ectopic calcification, in the walls of the retinal and glomerular vessels in many patients with diabetes mellitus, and in the walls of large blood vessels of patients with intimal fibrosis, and of animals before the development of experimental arteriosclerosis.[75-77] Histochemical studies indicate a decrease in metachromatic-staining material during wound healing in scorbutic animals[78] and in animals receiving cortisone.[79]

The pronounced metachromasia of the provisional zone of calcification is of special interest in view of the studies of Engel et al.[24] on calcium binding by connective tissue. These authors suggest the possibility that this metachromasia reflects "disagglutination" of the large colloids, with decrease in their charge density and release of calcium ions, thus favoring the formation of calcium phosphate crystals. Howard and his associates[76] have observed that metachromasia has also been found to be a characteristic of the "matrix" of certain kidney stones and in sites of ectopic calcification, suggesting that the areas of increased metachromatic staining represent sites of calcium binding.

In interpreting data based on histochemical evidence alone, one must bear in mind the evidence that metachromasia is by no means specific for the sulfated acid mucopolysaccharides. The reaction is also produced by nucleoproteins, hyaluronic acid in high concentrations and polymetaphosphates.[80,81]

Chemical Studies of Tissues

In patients with certain pathologic states chemical analyses of tissues for polysaccharide content have been performed. Analyses of areas of the involved skin of 2 patients with pretibial myxedema have demonstrated a much greater concentration of hyaluronic acid than in the uninvolved skin.[82] After thyroidectomy, guinea pigs and rats manifest an increase in the concentration of hexosamine in the retro-orbital tissue.[83] This does not occur if the animals are hypophysectomized, suggesting a possible relation between the pituitary gland and hexosamine metabolism.

Quantitative studies performed on deposits of amyloid in human beings and horses with secondary amyloidosis have suggested that this material is a complex of several substances, since it contains glucosamine, galactosamine, uronic acid and several hexoses together with a large amount of protein.[84] The exact nature of these materials and the reason for their accumulation in this disease are not known.

Comparison of the composition of subcutaneous nodules in patients with acute rheumatic fever with the skin from corresponding areas in control patients indicate that both tissues contain the same carbohydrates: glucosamine, galactose, mannose and glucose. Nevertheless, the nodules contain much larger amounts of carbohydrate, in addition to collagen and elastin.[85]

As more information concerning the definition and quantitation of the carbohydrate components of normal connective tissues and body fluids becomes available, more definitive studies of the alterations

in disease are being undertaken. It is to be hoped that an understanding of the physiology of these components will clarify knowledge of the pathogenesis of some of the more stubborn chronic diseases.

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MEDICAL INTELLIGENCE

THE USE OF A POLYETHYLENE CATHETER IN PERICARDIAL PARACENTESIS*

JAMES A. FALLOWS, M.D.,† AND BERNARD H. PASTOR, M.D.‡

PHILADELPHIA

PERICARDIAL paracentesis is often a useful and necessary procedure, but its application has been limited by its danger.[1] Although there is relatively little risk from perforation of the ventricular wall, hemopericardium may result from injury to a coronary vessel or perforation of the thin-walled atrium. In addition to the hazard of the initial puncture, any movement of the needle or change in the position of the patient is attended by a risk.

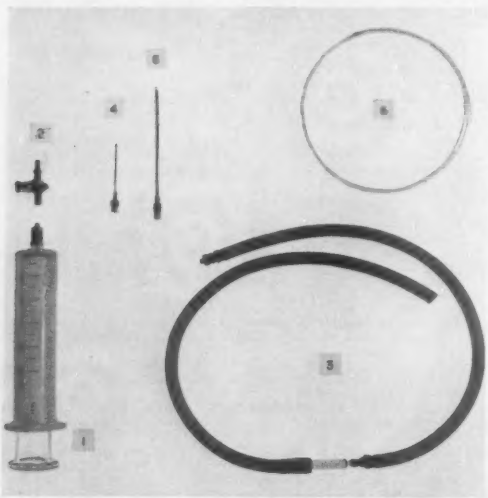

FIGURE 1. *Equipment for Pericardial Paracentesis. 1=50-cc. Luer-Lok syringe. 2=three-way stopcock. 3=Rubber tubing. 4=18-gauge needle. 5=No. 190 polyethylene tubing. 6=13-gauge needle.*

A simple and relatively safe technic for the aspiration of pericardial fluid has been devised. A polyethylene catheter is introduced into the pericardial sac through a paracentesis needle, which is then withdrawn, leaving the catheter in place. The patient may then be moved about freely so that the maximum amount of fluid can be removed.

The usual sites for pericardial paracentesis are adaptable to this procedure, although the more difficult ones (such as the epigastrium) are generally unnecessary. With routine aseptic precautions, the site of the puncture is prepared, and the skin and deeper tissues are infiltrated with procaine. Through a small skin incision, a short-bevel, 8-cm., 13-gauge needle connected to a syringe, is inserted into the pericardium in the usual manner.[1,2] When a free flow of pericardial fluid is obtained, the syringe is detached, and No. 190 polyethylene tubing with the tip directed downward is introduced through the needle so as to extend 5 to 10 cm. beyond the needle point. The needle is then withdrawn, leaving the catheter in

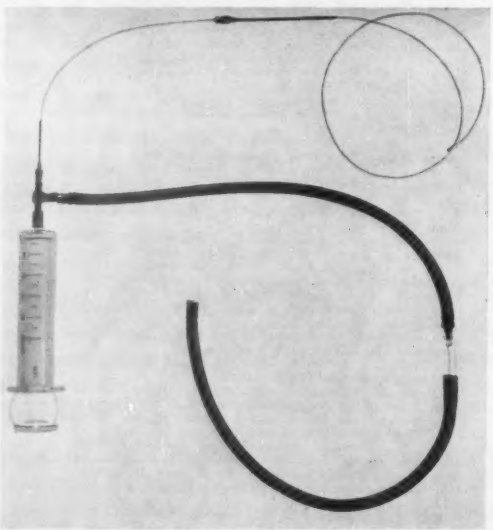

FIGURE 2. *Equipment Shown in Figure 1 Assembled for Use.*

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place. An 18-gauge needle is inserted into the end of the tubing, a three-way stopcock and syringe are attached, and the fluid is aspirated. A length of rubber tubing attached to the other arm of the stopcock permits the syringe to be emptied into a receptacle without the necessity of detaching it (Fig. 1-3). Any other aspirating device, such as a vacuum bottle, could equally well be employed with the catheter.

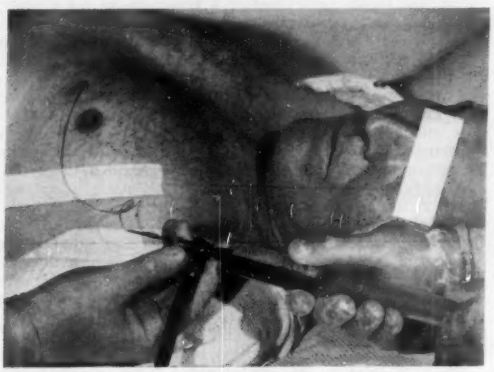

FIGURE 3. *Aspiration of Pericardial Fluid through the Polyethylene Catheter.*

If pericardial fluid is still present but the flow stops, several maneuvers should be attempted. A small amount of air can be injected to clear the tubing. The patient's position can be changed either by simple turning and bending or by means of the x-ray tilt table, so that the catheter tip is in a dependent position. The tubing can be rotated, or its depth adjusted to reach the fluid. If necessary, the tubing, which is not radiopaque, can be filled with 30 per cent Urokon, so that it can be visualized fluoroscopically or roentgenographically (Fig. 4).

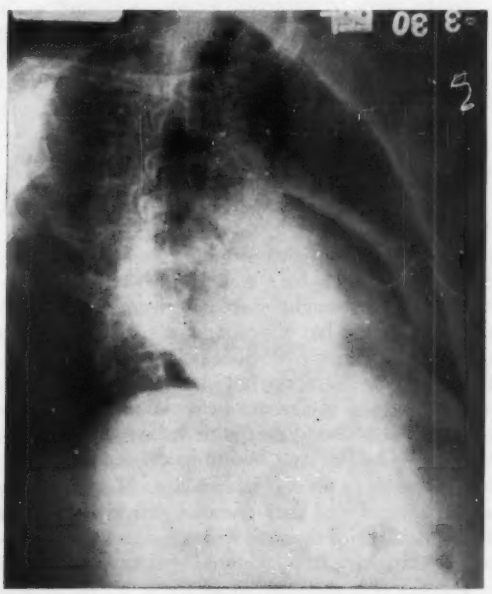

FIGURE 4. *Right Anterior Oblique X-Ray Film of the Chest, Showing the Catheter in Place Opacified with 70 per Cent Urokon.*

With this technic, pericardial aspiration is easier and more effective. The patient feels no discomfort throughout the procedure, and shows no untoward effects, despite changes of position and transportation by wheelchair to the x-ray department. An electrocardiogram with the catheter in place shows no premature beats or other changes.

SUMMARY AND CONCLUSIONS

Pericardial aspiration with a rigid needle is limited by the danger of perforation of the coronary vessels or myocardium.

A technic for the substitution of a polyethylene catheter for the needle is described.

This technic makes pericardial aspiration simpler, safer and more effective.

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MORE GIANTS IN THE EARTH

THE following random harvest, gleaned from the *Boston Medical Intelligencer,* published in 1825, pertains to two eighteenth-century fellows of the Massachusetts Medical Society who became eminent doctors afield. It comes to the *Journal* from Dr. Lawrence R. Dame, of Greenfield.

> His Excellency, Dr. WILLIAM EUSTIS, Governor and Commander in Chief of this Commonwealth, departed this life on Sunday last, at seven o'clock, in the seventy-fifth year of his age. He has been in public life for half a century, commencing his career at Cambridge in 1775, as a surgeon in the American army. In 1787, he was appointed surgeon-general to Lincoln's forces, raised to suppress Shays' insurrection, and was surgeon, adviser and warrior during the campaign. Since the adoption of the Federal Constitution, he has been generally employed in public life. He has represented Boston in the Legislature of this Commonwealth for several years; then was sent to Congress from the district of Suffolk — has been Foreign Minister, Secretary at War, Representative of Norfolk, and has been twice elected to the office in which he died, Governor of the Commonwealth of Massachusetts. — The heroes of the revolution are falling around us as the last leaves of the tree in the autumnal blast. — *Gazette.*[1]

> The Hon. JOHN BROOKS, M.D. late Governor of Massachusetts, departed this life at his residence in Medford, about 2 o'clock on Tuesday morning last, aged 73 years. This venerable and deeply lamented Physician, continued the active duties of his profession until confined by the Influenza, which terminated an earthly career most honorable and useful, and opened to him that light which smiles on the last moments of the good. Notwithstanding

the faithful manner in which he has uniformly executed the important political trusts committed to him, he continued to preside at the meetings of the Massachusetts Medical Society, and in the more private walks of life to remove the pain and suffering of all around him, and he felt amply compensated for these services by the love and respect of his numerous friends, and the consciousness of doing good. No one can regard the last years of the life of Dr Brooks, without saying in his heart — Oh for the old age of a christian scholar![2]

Precisely at one o'clock, John Dixwell, M.D. of Boston, commenced delivering a highly finished eulogy on the late lamented President of the Society, his Excellency John Brooks, M.D. of Medford. In point of language this was a well-written production; but it every where discovered a kind partiality, which must have been apparent to the audience. The names and characters of most of those members of the society, who have been distinguished in the service of their country, were portrayed in strong and sweet-flowing sentences, but the author appeared studiously to avoid even an allusion to the memory of the late Governor Eustis, who was also a fellow of the society. Surely such neglect could only be the result of downright calculation, as illiberal as it was ungenerous. Doctor Eustis was an able and accomplished Physician, as well as a statesman; but we must look to some other source for the eulogy on a man who has done honor to the profession in which he was once arduously engaged, and who will live in the memory of Americans, when many of his contemporaries will be forgotten.

By this discourse we are informed that Dr Brooks was a native of Medford, where he studied his profession with the celebrated Dr Tufts, under whose tuition he was placed at the age of about fifteen, and with whom he continued till his twenty-first year. He then commenced the practice of medicine in Reading, under favorable auspices, and was soon after married. The war taking place soon after, Dr Brooks was elected captain of a volunteer company, and from this post he was gradually promoted to the command of a regiment, as his military knowledge and accomplishments were made known to his superiors. He was the particular friend of Baron Steuben, and enjoyed the complete confidence of General Washington, who bestowed many marks of affection upon him, in appointing him to several important stations. After the close of the revolutionary struggle, Dr Brooks, by the earnest solicitation of his preceptor, who had now become infirm, entered upon the duties of his profession again, in his native town, where he remained the rest of his useful life, universally beloved by all classes of citizens, both at home and abroad. There is scarcely a literary or benevolent society, of character, in the United States, of which he was not elected a member. The university of Cambridge, many years since, conferred on him the honorary degree of Master of Arts, and subsequently those of Doctor of Medicine, and Doctor of Laws. He was seven years, in succession, Governor of this State, and only relinquished the cares and perplexities of public life, when his infirmities would no longer enable him to undergo the fatigues of such laborious duties. — Such is an outline of the character and life of this lamented man, who lived beloved and respected, and died at a good old age, universally regretted.[3]

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41461

Presentation of Case

A twenty-seven-year-old woman of French extraction entered the hospital complaining of amenorrhea, hirsutism and obesity.

Seven years before admission the patient, who had been married for three years, consulted a physician because of failure to become pregnant. She received numerous hormone injections. Subsequently, she was delivered of a stillborn infant and of an infant who lived for two days, each at eight months' gestation, and of two full-term normal infants. The last three deliveries were by cesarean section, and during the final one, three years before admission, the fallopian tubes were tied. According to the patient she was unable to nurse her last infant because her milk, though profuse, was "not rich enough." Three months post partum the patient had a normal period, followed by two or three periods occurring at the expected dates, but characterized by spotting instead of the usual flow. After this there were no more periods. About the time of onset of amenorrhea, she noticed the appearance of hair on the lips and cheeks, which required shaving twice a day. In the two years before admission the weight increased from 155 to 230 pounds. In the last six months she dieted, but was unable to lose weight. She experienced no loss of libido. There were no hot flashes. The menarche was at the age of eleven. Before the present illness periods had occurred every thirty days and lasted for six days. The flow was said to have been normal.

The patient's parents were hairy. Her father had died at the age of sixty-seven of arteriosclerosis and diabetes. One of 6 sisters had a hysterectomy at the age of thirty-five for carcinoma of the uterus.

Physical examination revealed a young woman, 157.5 cm. in height and weighing 233 pounds. The obesity was most marked in the abdomen and thighs. There was a prominent dorsal fat pad. A stiff beard, a heavy growth of dark hair on the forearms and thighs, and a lesser growth on the abdomen were present. Temporal hair recession was absent. The breasts were large and pendulous. There were no

striae. The lower abdomen was slightly tender, especially on the right side. Pelvic examination revealed apparent slight enlargement of the clitoris and a moderate vaginitis. The uterus was in the anterior portion of the pelvis and was somewhat small. No masses were palpable on pelvic, rectal or abdominal examination.

The temperature was 98.6°F., the pulse 92, and the respirations 21. The blood pressure was 110 systolic, 75 diastolic.

Urinalysis was negative except for a + test for albumin and a sediment containing 40 white cells and 15 red cells per high-power field. Examination of the blood revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 10,750, with a normal differential. An eosinophil count three hours after a meal was 384 per cubic millimeter. A glucose tolerance test revealed a fasting blood sugar of 107 mg., a level of 187 mg. at half an hour, 186 mg. at one hour, 97 mg. at two hours and 66 mg. per 100 cc. at three hours. There was no glycosuria. Urinary 17-ketosteroid levels on four successive days ranged from 9.6 to 13 mg. per twenty-four hours. Urinary estrogen levels on four successive days ranged from 79 to 122 microgm. per twenty-four hours. FSH (follicle-stimulating hormone) urinary excretion tests were negative for 96 and 192 mouse units per twenty-four hours on two occasions. A vaginal smear was reported as "atrophic." An attempted endometrial biopsy yielded no tissue. A barium-enema examination was negative. Presacral retroperitoneal air injection gave excellent visualization in the x-ray films of the adrenal glands, which appeared normal in size and shape. Culdoscopy showed numerous adhesions in the pelvis. The uterus and right tube appeared normal. The left tube and ovary were not seen. The right ovary was only partially seen, and this portion did not seem enlarged or irregular.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Anne P. Forbes*: I think all the important information in the history is given in the first sentence: "A twenty-seven-year-old housewife of French extraction entered the hospital complaining of amenorrhea, hirsutism and obesity." Most of the other data can be eliminated as not helpful. Although the patient had consulted a physician for sterility and received hormone injections, sterility turns out not to have been present because she subsequently had four pregnancies. She was delivered of a stillborn infant and another that lived for two days. The only endocrine condition for which that would be useful information is diabetes, but later we find that she did not have diabetes and she subsequently had a normal baby. She was unable to nurse the infant because the milk was of the wrong quality. That is maintained by innumerable normal women and is not useful. After the pregnancy the periods became scanty, and after two or three scanty periods, they stopped altogether. That I consider a useful fact. About the same time, at the age of twenty-four, she noticed the appearance of hair. The age at which she noted the appearance of hair is important. The weight increased from 155 to 230 pounds in about two years. A weight of 155 pounds for her height was already plump. The gain was impressive but not alone very useful. She dieted and could not lose the weight. That is not helpful. In theory the patient whose obesity is on the basis of adrenocortical hyperfunction ought to lose weight more rapidly on a diet than the normal person; actually, the determining factor is always the way in which the diet is followed. She had no loss of libido; loss of libido is not characteristic of any of the hirsutism-producing syndromes that I have to consider. There were no hot flashes; I do not suspect the menopause as the cause of hirsutism. That the periods were regular to the age of twenty-four, I do think is something to remember. The clitoris was apparently slightly enlarged. I imagine that of 5 observers, 3 said it was enlarged, and 2 said it was not. At any rate that is not going to help since it was not clearly enlarged. There was no hypertension, which is useful in ruling out too much production of adrenal corticoid. The hemoglobin of 15 gm. per 100 cc. I think ought to be mentioned. Dr. Philip H. Henneman pointed out that that is the average normal value for a male but is higher than the average for a female. Most females with virilizing syndromes tend to have hemoglobin levels that are normal for males. The white-cell count was 10,000, with a normal differential. Dr. Scully, would you mind giving me the percentage of lymphocytes?

Dr. Robert E. Scully: The lymphocytes were 35 per cent.

Dr. Forbes: That percentage with the high eosinophil count is further evidence against too much adrenocortical hormone. The negative glucose tolerance test and the absence of high blood pressure add to the battery of tests negative for Cushing's syndrome.

The urinary estrogen level of 79 to 122 microgm. is the level seen in a normal cyclic woman. The FSH was not increased. That is not useful since I do not suspect the menopause. What I should like to know is whether it was decreased. The barium-enema and air-injection examinations showed two adrenal glands, normal in size and shape. In only 1 case have I clearly seen the shadow of an adrenal tumor in the films after perirenal air injection. That patient had a cyst of the kidney and bilateral hyperplasia of the adrenal glands but no adrenal tumor. This examination does not rule out the presence of an adrenal tumor although it is weight against it. Only part of one ovary was visualized.

*Assistant physician, Massachusetts General Hospital.

The first possibility that I have to rule out is that this patient had no endocrine disease. She had rapidly accumulated obesity, and that alone can give rise to amenorrhea of long duration. The amenorrhea can disappear, with weight reduction. That is seen in entirely normal women who have gained weight through change in their living habits. Since in this patient the amenorrhea occurred before the obesity I should suspect that it was not due to the obesity. The hirsutism may not have been abnormal. She was of French extraction, and the family was hairy. The hirsutism that is constitutionally normal for a woman comes on at the same age that hirsutism that is normal for a man comes on — namely, the moustache in the early teens, the beard in the late teens, and chest hair in the early twenties. Often, a patient who has had gradually increasing hirsutism from the age of fifteen to twenty-five has claimed that the hirsutism has grown much worse in one year or has been present for only a year. Often, however, she has noticed it then for the first time, or it has just then reached a level that distresses her. Careful questions will reveal that it has been progressing steadily ever since puberty and is constitutional for her. Since I cannot question this patient, I shall assume that the hirsutism was new and striking and represented an abrupt change and that therefore amenorrhea, hirsutism and obesity represented some disease, not merely the normal constitution of the patient.

Having decided that she had too much androgen, I have four possible sources to choose among. The two places that androgen comes from are the ovary and the adrenal gland. In each there may be a diffuse disease or a tumor. With ketosteroids ranging from 9.6 to 13 mg. I do not believe that she had diffuse hyperplasia of both adrenal cortexes. At least in our records, we have no patients with virilizing syndrome and bilateral adrenal hyperplasia who have normal ketosteroids. That does not mean that she did not have too much androgen, for the level of the ketosteroids was the normal one for a normal male and is sufficient to account for virilism, but is not enough above the normal level for females to support a diagnosis of adrenal hyperplasia. It suggests that the androgen resembled testosterone, which is more virilizing per milligram of ketosteroid excreted as metabolite than other androgens. I shall decide against adrenal hyperplasia partly for the above reason and partly for the reason that adrenal hyperplasia does not appear suddenly.

We also have not seen any cases of benign adrenal tumor producing virilization, with normal ketosteroids. We have seen some that produced Cushing's syndrome and also some malignant adrenal tumors, with normal ketosteroids, including a young woman whose disease began shortly after pregnancy at about the same age as this patient's. Later on, as the carcinoma developed, the ketosteroids in that patient became higher. A few adrenal cancers even terminally never produced very high ketosteroid values, but these were not accompanied by a great deal of virilism. I should think that an adrenal tumor was unlikely. One other reason why I think that she did not have an adrenal tumor is that she had no signs pointing to an overproduction of any adrenal hormone other than androgen. She had no sign of hyperproduction of glucocorticoids or mineralocorticoids—no diabetes, no striae, no polycythemia and no decrease in eosinophils.

I shall now discuss a diffuse process or a tumor in the ovary as the source of this patient's excessive androgen. By a diffuse virilizing process in the ovary, I mean different processes such as theca luteinization and polycystic, large, pale ovaries. These are not distinguished from each other by authorities. I shall consider them as a group along with hilus-cell hyperplasia, another virilism-producing ovarian process, and speak of them as one disease.

About ten years ago I looked up 100 cases of patients who came to this hospital complaining of hirsutism. Of the 100, 70 or 80 per cent also complained of amenorrhea and obesity. Except in the few who had a tumor somewhere, the symptoms began at the time of their puberty, as constitutional hirsutism will, and the periods were irregular from the age at which hair developed. A few of those patients were explored; the findings depended on the site of exploration. For example, if the ovaries were explored, some were said to show the Stein–Leventhal, large, pale ovaries and some to have theca luteinization of the ovaries. Clinically, they were exactly the same. Dr. Fuller Albright asked one of these patients if she were distressed enough to have an operation. She said, "Yes." He said, "Are you willing to have two?" She replied, "Yes." He said, "Three?" She said, "Yes." In that patient both adrenal glands as well as the ovaries were explored. The adrenal glands showed a reticular zone larger than normal, and the ovaries showed theca luteinization. The disease not only may be diffuse within the ovary but also may be secondary to a pituitary hyperfunction and involve both the ovaries and the adrenal glands. There is no real understanding of constitutional amenorrhea and hirsutism. It is what Stein and Leventhal have written about, I think, and probably is associated with theca luteinization.

I cannot tell, from seeing a patient with too much androgen, what cell is producing the androgen. The only basis I have for preferring ovarian tumor to one of the diseases in this group is the history of its striking onset in a previously normal person. The ketosteroids in the group of at least 100 patients with the amenorrhea-hirsutism-obesity syndrome averaged significantly higher than those in a similar group of normal cyclic women, but in only a few were the ketosteroids outside the normal range. In the cases similar to the one under discussion, the ketosteroids were around 12 or 10 mg. Would a virilizing ovarian tu-

mor necessarily produce higher ketosteroid levels than the diffuse ovarian diseases? They do not have to. We had seen cases of arrhenoblastoma with normal ketosteroids. We also followed 1 patient with a luteoma through a period in which the ketosteroids were not diagnostically elevated, although later they were.

If I choose a tumor, which tumor to choose is guesswork because the patient may have grown a beard as the result of androgens from any number of different sources. In general the luteomas are more likely also to cause the production of adrenocortical-like hormones other than androgens. They are more likely to cause a Cushing syndrome with the virilization than the arrhenoblastomas, which can produce both the hormones that the testis produces, and reproduce the picture seen where normal testicular tissue is present. Arrhenoblastoma can produce a hormone that inhibits FSH and might be excreted as estrogen and a hormone like testosterone, which is very virilizing for the amount of ketosteroids found in the urine. For that reason I shall choose an arrhenoblastoma. The left ovary was not seen; the right was seen and was not large (which is another point helpful in ruling out the Stein–Leventhal syndrome). If I place the tumor on the left, that tenderness in the right lower quadrant will not be helpful. I am forced to choose an arrhenoblastoma of the ovary that was not seen — namely, the left ovary.

Dr. Patricia H. Benedict: This patient reminds me very much of 2 patients whom we saw recently in the Ovarian Dysfunction Clinic; those patients had hyperthecosis in the ovary, — that is, theca-cell luteinization, — and I should bet on that.

Dr. Philip H. Henneman: I do not know of any cases of hilus-cell adenomas or hyperplasias that have occurred much before the menopause. Thus, this patient's age might be evidence against that extremely rare syndrome. Years ago we had a patient with a dysgerminoma of the right gonadal region who was slightly virilized; her ketosteroid excretion was not increased. She had no gonad on the left side, which is not uncommon in dysgerminoma. Perhaps dysgerminoma is a possible diagnosis in the patient under discussion since no left gonad was seen.

About ovarian causes of virilism, at the Laurentian Hormone Conference[1] this year there was considerable discussion among the steroid chemists of the possible conversion of androgen to estrogen by the ovaries. Indeed, the suggestion was made that androgen might be the precursor of ovarian estrogen. If androgen is normally formed by the ovary and then converted to estrogen, it is not unreasonable to guess that abnormal ovarian tissue might secrete an "incomplete" estrogen with androgenic activity. Would Dr. Engel like to clarify that for us?

Dr. Lewis L. Engel: Perhaps Dr. Baggett will; he has been working on this problem.

Dr. Billy Baggett: We do not have any evidence that this is necessarily the normal pathway for the formation of estrogen. We do know, however, that this transformation can take place. The transformation has been demonstrated in normal human ovaries as well as in certain cases in the adrenal gland. These tissues have been shown to convert testosterone to biologically active estrogens. Whether this is the normal pathway for the formation of an estrogen or just how widespread this potentiality is I do not know. We need other types of observations before we can answer that.

Dr. Engel: The slight elevation in the ketosteroids is perfectly consistent with excessive production of one or more steroids and a compensatory decrease in the production of other steroids. We have seen patients in whom the ketosteroids of adrenal origin were elevated well above the normal limits. Although the total ketosteroids were within normal limits, in a patient with luteoma we found a marked increase in androsterone excretion. Androsterone, of course, is a well recognized metabolite of testosterone but could also have been derived from some other ovarian precursor. I should not like to generalize from these scanty observations.

Dr. Scully: Was this "luteoma" a masculinizing tumor, Dr. Engel?

Dr. Engel: Yes; it was.

A Physician: I should like to ask why the hirsutism and amenorrhea were supposed to be due to androgens if there was no temporal recession.

Dr. Forbes: I took the history's word for it that this patient never had any beard and was suddenly growing a very impressive one. A considerable number of normal males do not have much temporal recession, and even those who do take a while to acquire it. She had the beard for three years. It is about three years after puberty that most boys have a marked temporal recession. Some do not have much chin hair either.

Dr. Scully: Regarding hilus-cell hyperplasia, and tumors, I believe that in several cases in the literature,[2,3] although the diagnosis was not made until late in life, manifestations of virilism had appeared much earlier.

Clinical Diagnosis

?Stein–Leventhal syndrome.
?Arrhenoblastoma.

Dr. Anne P. Forbes's Diagnosis

Arrhenoblastoma of ovary.

Anatomical Diagnosis

"Ovarian hyperthecosis."

Pathological Discussion

Dr. Scully: A pelvic exploration revealed both ovaries to be enlarged and enclosed by thick, white

capsules. On incision multiple follicle cysts were seen just beneath the capsules. A wedge was resected from each ovary. Microscopically, the capsules were sclerotic. The follicle cysts and several atretic follicles were surrounded by thick mantles of theca cells loaded with lipoid (Fig. 1). Likewise, throughout the cortical stroma were numerous nests of lipoid-filled cells similar to, but larger than, the theca cells (Fig. 1). Dr. Richard B. Cohen, of our department, has done histochemical studies on these tissues and has found that the cells lining the follicles and those composing the stromal nests contained material that gave histochemical reactions identical to those of the zona fasciculata of the adrenal cortex. This suggests that these cells were putting out some type of steroid.

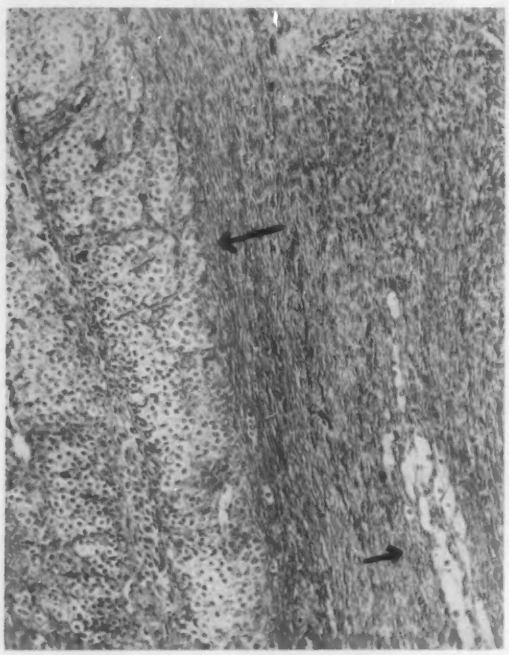

FIGURE 1. *Photomicrograph of Ovary.*
The upper arrow points to a layer of large lipoid-filled theca cells lining an atretic follicle. The lower arrow points to a nest of larger lipoid-laden cells in the stroma.

This combination of pathological findings is called ovarian hyperthecosis[4] by most authors. Another term for it is luteinization of the ovarian stroma.[5] Neither term is particularly good, however; so little is known of the nature of the disease that the ideal name is not yet in sight.

Most of the cases we have seen in this hospital have been associated with virilization. In 1[6] there was suggestive evidence of adrenocortical hyperplasia as well as hyperthecosis. In some of the cases in the literature[7] the predominant clinical picture has been one of metropathia hemorrhagica, with periods of irregular and often excessive bleeding alternating with periods of amenorrhea. Indeed, a few of these patients have had cystic hyperplasia of the endometrium, and a rare one endometrial carcinoma.[8] I think the last association is of great interest because the sister of the patient under discussion is said to have had cancer of the uterus at the age of thirty-five, a comparatively young age for this disease. I wonder whether her ovaries may not have looked similar to this patient's.

Study of our cases has so far failed to separate sharply the Stein–Leventhal syndrome and hyperthecosis. Most of our patients with the stromal change characteristic of hyperthecosis have shown frank virilism whereas those with simple Stein–Leventhal ovaries have usually had hirsutism at most. I think perhaps we shall have to await the results of Dr. Engel's hormone assays on large numbers of patients before we can hope to separate these two syndromes, if, indeed, they are separable.

DR. HENNEMAN: Can you tell us about the follow-up findings and in particular what the 17-ketosteroid excretion was after operation?

DR. SCULLY: The follow-up period on the patient is too short to be of any value, and we do not know what will happen to the 17-ketosteroids as yet.

DR. HENNEMAN: This seems to be a crucial observation about whether the symptoms were due to the abnormal ovary or whether they were due to equally abnormal adrenal glands.

DR. SCULLY: I think that is very true. Shippel,[7] who is a gynecologist at the University of Witwatersrand in Johannesburg, has recently reported a large series of patients with this syndrome in whom he has obtained good results in restoring normal menstrual function by wedge resection of the ovaries. He has had somewhat less success in relieving the hirsutism and other evidences of virilism.

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CASE 41462

PRESENTATION OF CASE

A sixty-two-year-old Italian-born woman entered the hospital complaining of pain in the right flank and back.

On the morning of admission she suddenly experienced the onset of sharp pain in the right flank and across the lower back on bending forward. The sharp pain persisted. The patient became nauseated and vomited several times. She was unable to find a comfortable position. During the day she urinated frequently but passed only small amounts. There was a burning sensation on micturition.

She had had 16 pregnancies, and 14 children living and well. Twelve years before admission she had a hysterectomy, oöphorectomy and appendectomy for unknown reasons. In the past she had had some belching and epigastric fullness.

Physical examination revealed a well nourished woman in acute distress. There was a firm, round mass in the right side of the abdomen, which was tender, extended from the costal margin to the umbilicus and moved with respiration. Liver dullness started at the fifth rib. There was marked tenderness of the muscle and tissues overlying the right flank and sacroiliac joint. Pelvic examination showed an amputated cervix, and a cystocele and rectocele.

The temperature was 99.8°F., the pulse 84, and the respirations 14. The blood pressure was 155 systolic, 75 diastolic.

Urinalysis revealed a pH of 6.5, negative tests for albumin, sugar and bile and a sediment containing 1 to 2 white cells and 10 to 12 red cells per high-power field. Examination of the blood disclosed a hemoglobin of 13.2 gm. per 100 cc. and a white-cell count of 14,700. A second white-cell count was 7100, with 52 per cent neutrophils, 39 per cent lymphocytes and 9 per cent eosinophils. The nonprotein nitrogen was 27 mg., the fasting blood sugar 102 mg., the bilirubin 0.9 mg., and the alkaline phosphatase 3.4 units per 100 cc. The prothrombin time was 74 per cent of normal. A urine culture was negative. A guaiac test on the stool was positive. X-ray films of the abdomen showed a large, round, calcified mass overlying the upper pole of the right kidney. The calcification had the appearance of a shell. Multiple phleboliths were noted in the pelvis. An x-ray film of the chest revealed a transversely enlarged heart and a tortuous aorta. The dorsal spine showed degenerative changes. An intravenous pyelogram revealed blunting of the renal calyxes on the right, particularly in the upper pole (Fig. 1). A nephrotomogram gave no additional information. Metastatic series of the skull and pelvis gave no evidence of metastatic disease.

On the twelfth hospital day an operation was performed.

Differential Diagnosis

Dr. Walter S. Kerr, Jr.*: A modern mother would think that this could all be explained on the basis of 16 pregnancies, but I doubt it. I might ask Dr. Hanelin to show the x-ray films.

*Assistant urologist, Massachusetts General Hospital.

Dr. Joseph Hanelin: There is a large mass, roughly 14 cm. in diameter, which seems to take its origin from the upper pole of the right kidney. The mass is irregularly calcified along the periphery and presents an irregular lobulated outline (Fig. 1). The right kidney is displaced downward. For some reason, although no dye was administered, the gall bladder can be seen. It is larger than normal and contains opaque stones. The intravenous pyelogram shows normal passageways on the left. On the right a moderate hydronephrosis is present, with a slight indentation on the superior calyxes. There is a suggestion of a small stone in the distal portion of the right ureter in several of these films, which may be

Figure 1. *Intravenous Pyelogram.*
A large, lobulated mass showing calcification of its periphery is present at the upper pole of the right kidney (arrows). The moderate right-sided hydronephrosis may be due to a small calculus in the distal ureter.

responsible for the hydronephrosis. The examination of the chest is essentially the same as recorded.

Dr. Kerr: Do you think that there is a suggestion of cysts within the cyst?

Dr. Hanelin: At the upper lateral margin of the mass there is a suggestion of a cyst that is budding from the main mass.

Dr. Kerr: Do you think that it is unusual to see such a large mass with so little change in the calyxes in the upper portion of the kidney?

Dr. Hanelin: More commonly there is more deformity, but this does not necessarily disprove its renal origin; the mass may have started in the periphery and extended away from the kidney.

Dr. Kerr: As Dr. Hanelin noted, there are several spots in the film that suggest stones in the lower

ureter. The severity of pain of which the woman complained certainly would fit with renal colic. The tenderness in the right flank was of the type present over a kidney that has been blocked by a stone in the ureter either at the time or shortly before the examination. The urinary sediment contained a few white cells, which apparently were not of importance inasmuch as the culture was negative. There were 10 to 12 red cells per high-power field, which, of course, also fits in with the picture of a small ureteral stone. About 15 per cent of the patients who come into the hospital with typical renal colic will not have any x-ray evidence of a stone in the ureter. Moreover, the stone may not be found in the urine even though the urine is carefully strained, because a tiny fragment of a stone, a millimeter or so in diameter, can cause as severe renal colic as one that is 8 or 10 mm. in diameter. I think that a renal stone, which had dropped into the ureter, was the explanation for the pain. There was no albumin, sugar or casts in the urine so that in view of the negative culture and the few white cells, I do not believe that she had a pyelonephritis or infection in the kidney — at least one that was draining into the pelvis.

The chemical levels were all within normal limits. I rather wonder why some of them were obtained. I am glad they were normal and do not add confusion to the picture.

Lumps in the kidney are always a challenge; commonly, one is not able to tell before the patient is operated on what the lump is. I am reasonably certain that this mass in the kidney was an incidental finding and not connected with the pain, increased temperature or elevated white-cell count. The white-cell count of 14,700 on admission was certainly high for a blocked, uninfected kidney, but possibly it was the result of dehydration inasmuch as the pain had caused nausea and some vomiting. Occasionally, a vessel in the cortex of the kidney will rupture spontaneously and will give rise to a picture similar to the one that this woman had — namely, pain in the flank, usually not as severe as she had — and a white-cell count of 14,000 or even 25,000. However, with a hemorrhage of large size, the hemoglobin is likely to be lower than was found in this patient. Therefore, I am fairly certain that this was not a rupture of a vessel, either in the mass or in the kidney itself, with hemorrhage.

What may the mass have been? Dr. Hanelin seems certain that it was attached to the kidney. Some oblique views would lead one to be fairly certain of that. However, it is possible that it arose in a retroperitoneal structure, such as the adrenal gland. Some adrenal cysts, although I never have seen one, apparently can show calcification, not unlike that seen here. Of course, adrenal tumors also calcify. Usually, they show blotchy calcifications rather than a definite rim of calcification. Cysts of the liver have been reported to push the kidney downward, but they have to arise in an unusual fashion to do it. Retroperitoneal tumors — sarcomas of various kinds — could present this picture. I have not seen any in which the calcification had the pattern noted here. Solitary cysts of the kidney usually do not calcify, but when they do, the calcification is in the rim.

Hypernephromas frequently grow so rapidly that areas of necrosis develop within them and become calcified. I cannot recall having seen any calcifications in the periphery. Dr. Hanelin, have you seen any hypernephromas that were calcified around the edge?

DR. HANELIN: I think I have in the past seen one or two, with calcification along the periphery although generally the calcification is within the substance of the hypernephroma. Solid tumors will certainly do that. You mentioned an adrenal origin. It would be impossible for me to differentiate between an adrenal and a renal origin in this case. I have seen an adrenal cyst that was partially calcified, although that was smooth in outline.

DR. KERR: A tuberculous kidney will sometimes nephrectomize itself by thorough calcification. In those kidneys the calcification outlines the kidney in the periphery. I have never seen extensive calcification of that nature in one part of the kidney, however. Usually, if the process is so extensive, it involves the entire kidney.

Another possibility to consider is echinococcus cyst. These are rare in this country but are very common in other parts of the world. Uruguay and the Argentine apparently have the greatest number. Surraco[1] reported 29 cases of echinococcus cyst of the kidney. This disease is caused by small tapeworms that are usually found in dogs or wolves and possibly in cats. They escape in the dog's feces and are picked up on the hands — usually of children, who play with the dogs — and get into the mouth. Most of the tapeworms or their eggs get into the liver, but occasionally they apparently go through the lungs into the systemic circulation and land in the kidneys as well as other places, such as livers. Usually, if the kidney is involved, the echinococcus cysts are unilateral. Also, the patients do not have symptoms until the age of thirty-five or possibly forty-five. The symptoms to a large extent depend upon whether the cyst connects with a calyx and drains into the kidneys or whether it remains a closed cyst. I think that in the patient under discussion the mass was a closed echinococcus cyst. Surraco included x-ray films of a number. In every film — about 10 — the cysts were in the upper pole. Whether that is a constant feature or not, I do not know. The x-ray appearance was characteristic: if the cyst was connected with the kidney pelvis, the dye entered the main cyst and outlined the daughter cysts, giving a honeycombed appearance; in some cases, apparently, there is a space between the cyst and the kidney, which has a crescent-shaped appearance on retrograde pyelography. Retrograde pyelograms were not done in the case under discussion.

Whether or not there was a space there, I am not certain. When it is present, the diagnosis is easily made. Several tests can be done, the intradermal test or the complement-fixation test if fluid from other cysts is available for injection. The treatment for this disease in general is conservative — namely, a partial nephrectomy or marsupialization of the cyst after formalin has been put in the cyst to kill the daughter cysts.

It is reported that sometimes these cysts, as the result of compression of the kidney, will block off part of the kidney, giving the picture of renal colic — microscopical hematuria, and pain in the flank. There is a possibility that this patient did not have a ureteral stone, and that the tenderness and the pain were due to the compression of the kidney by this mass. If these cysts do communicate with the renal pelvis and some of the daughter cysts escape, they will cause hematuria and renal colic. However, the urine apparently did not contain evidence of that — and this provides further evidence that the cyst probably was closed.

I believe that this patient had an echinococcus cyst and a ureteral stone.

DR. BENJAMIN CASTLEMAN: Would anyone like to ask Dr. Kerr any questions?

DR. RICHARD V. WILSON: I should like to ask him how often echinococcus cysts in the kidney are associated with cysts in the liver.

DR. KERR: I am sorry; I do not know. Somebody wrote that 70 per cent of people who have echinococcus disease are likely to have cysts in the liver; only 3 per cent have cysts in the kidney.

CLINICAL DIAGNOSIS

Renal-cell carcinoma, with calcification.

DR. WALTER S. KERR, JR.'S, DIAGNOSES

Echinococcus cyst of kidney.
Ureteral stone.

ANATOMICAL DIAGNOSIS

Echinococcus cyst of kidney.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation the kidney was removed in its entirety. The surgeon found the upper pole adherent to the surrounding structures, but was able to separate it easily and removed the kidney in the usual way. As is evident from this photograph of the specimen, Dr. Kerr was correct in his diagnosis (Fig. 2). The echinococcus cyst, which measured about 12 cm. in diameter, had a very thick capsule, that in many places was markedly calcified. It was a closed cyst and markedly compressed and pushed down the calyxes. It replaced about two thirds of the kidney. The rest of the kidney was perfectly normal. When opened the cyst contained many daughter cysts from 0.2 to 3 cm. in diameter. Microscopically, the wall was thick, with the characteristic chitinous membrane that apparently protects the germinal epithelium. Pathognomonic brood capsules and scolices were evident in many of the sections. A paper from New Zealand,[2] where this disease is quite common, reported that in most cases of echinococcus disease of the kidney, the kidney alone was involved. Such patients have no trouble after removal of the kidney. They do not as a rule have cysts in the liver. A common laboratory finding in cases with echinococcosis is eosinophilia; this patient had an eosinophil count of 9 per cent in the peripheral blood.

FIGURE 2.

DR. ALLEN G. BRAILEY: Were there any ureteral stones?

DR. CASTLEMAN: None were mentioned.

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CONCERNING THANKSGIVING

IT seems impossible that any new changes could be rung, especially in a publication of such limited scope as a medical journal, on subjects so hackneyed and so time-worn, even if so time-honored, as the perpetually recurrent annual festivals. And yet it is being done week after week and year after year in the various nonmedical journalistic presses of the world with a fidelity that must indicate something or other in respect to the steadfastness of human nature.

There will appear this week and next, according to the more or less accurate statistical averages that have been conjured up, somewhere in the vicinity of 35,000 or 135,000 original Thanksgiving editorials or other literary allusions — in addition to this current contribution — to that celebrated occasion. A corresponding efflorescence will take place in chronologic proximity to Christmas; the first babies to be born on New Year's Day will be hailed like temporary princelings, and similar verbalizations will be associated with the birthday of the Father of his Country and, coming also in February, with that of its most conspicuous advocate of unionism.

Other happy events receive their reiterative accolades. On the local scene, amid the wet snows of March, many pungent paragraphs appear each year in reference to the driving out from Boston of the British by St. Patrick, — some call it Evacuation Day, — and so each of the holidays up to and including the November paradox that still stirs nostalgic memories of the peace of 1918 receive their share of printer's ink. In giving thanks for Thanksgiving, one may be thankful also for the other opportunities for journalistic exploitation that have been overlooked.

It is particularly fitting that any New England publication, even of medicine, should have adopted the custom of finding annually something different to say in praise of giving thanks — for it is to New England that the origin of the gracious gesture has been universally attributed. In pioneer days this indigenous attribute of gratitude had many foci of proliferation, and the pilgrims were pious and thanksgiving people. They had escaped from the perils of the sea and diverted the suspicions of the Indians. They had found solid ground under their feet and constructed roofs to cover their heads, and wild turkeys in abundance gobbled up the parched corn that the settlers regularly dropped as markers by which to retrace their steps to the village, and were thus lured to the primitive chopping blocks of Plymouth; the turkeys, that is.

This relative security has been lost in recent years, leaving to New Englanders as a major source of thanksgiving the fortitude with which they have been able to endure the various climatic catastrophes that have been visited upon the region. It has been claimed that Thanksgiving originated in Virginia, but no one has appeared to substantiate the claim,

nor did the early settlers along the James leave any record of their opinion on the matter.

MASSACHUSETTS MEMORIAL HOSPITALS

It is a privilege this week to join the Massachusetts Memorial Hospitals in celebrating the hundredth anniversary of the incorporation of the institution from which they have developed. Its history, considering as a single organization the aggregation of units that comprise the hospital, is presented elsewhere in this issue of the *Journal* by Dr. Henry J. Bakst, chief of the hospital's Home Medical Service and professor of preventive medicine at Boston University School of Medicine.

Identified at its inception and for a number of years thereafter with the system of medical practice elaborated by Samuel Hahnemann, the Massachusetts Homeopathic Hospital was incorporated on May 19, 1855, under a charter issued to the Massachusetts Homeopathic Society. Its establishment was delayed, however, and, to a degree, its place was taken by the Massachusetts Homeopathic Dispensary, incorporated in 1856 and opened in 1857. For nearly a score of years the Dispensary served the needs of the Homeopathic Society as well as such an establishment could; in 1871 the hospital charter was revived, and plans were laid for its construction. The interest and energy that went into the raising of the money is attested by the proceeds of $76,000 from a fair undertaken by the Ladies' Aid Association.

The building was opened in 1876 on the present site of the hospital on East Concord Street, and since that time has been a going and a growing concern, identified from its beginning with Boston University. As others of the mid-nineteenth-century crop of medical schools were vanishing from the scene, Boston University had acquired its own school in 1873 by taking over the New England Female Medical College, which had been established in 1848.

The Massachusetts Homeopathic Hospital never languished in its popularity among Boston's benefactors, or faltered in its growth. Since its beginning a succession of five memorial buildings have been added to the original hospital, leading to its present unique group and, in 1929, to the adoption of the present name. Those who have found some confusion in the designation of a single organization by a plural name need only to be reminded of the strength and unity that their country has acquired under such a mutual arrangement, and its Latin motto.

ANTIBIOTIC MONOGRAPHS

During the past few years several thousand papers have been published each year, and an imposing number of books have appeared concerning antimicrobial therapy, the more recent ones dealing mostly with antibiotics. These papers and books have either presented or attempted to correlate the large mass of information that has accumulated so rapidly in this important area of medicine — important equally to the medical profession and to the great pharmaceutical and chemical industry. Some of the books have dealt with the general field; others have dealt with individual antibiotics or groups of chemotherapeutic agents, and still others have given attention to more basic problems involving the mechanisms of their action.

In this country Dr. Henry Welch, director of the Antibiotics Division of the Food and Drug Administration (now under the Department of Health, Education and Welfare), has taken the lead in an attempt to collect and organize the available information in this field. First he sponsored and organized antibiotic conferences, at which workers in industrial and in noncommercial laboratories, as well as clinicians and clinical investigators, could present and discuss all aspects of problems in this field. Then, with the co-operation of Dr. Felix Martí-Ibáñez, he sponsored and edited the special journal, *Antibiotics and Chemotherapy*, and its more recent clinical counterpart, *Antibiotic Medicine*. Together, they have also reinstated the antibiotic conferences on an annual basis and are publishing the papers presented at these conferences in volumes that, judging from the first two that have already appeared under the titles *Antibiotics Annual, 1953-1954* and *1954-1955*, seem to be of rapidly increasing size. With Dr. Charles H. Lewis, Dr. Welch also presented a comprehensive volume, *Antibiotic Therapy*, which he later edited in a revised edition as *Principles and Practice of Antibiotic Therapy*; the latter contains authoritative summaries of the available information about the more important and widely available antibiotics and their uses in the management of various groups of the common infectious diseases. A small volume, *The Manual of Antibiotics, 1954-1955*, contains a compendium of the preparations, a therapeutic index, lists of the generic and trade names and of the producers of various antibiotic preparations.

Antibiotic Monographs is the most recent series of publications being undertaken under the editorial direction of Drs. Welch and Martí-Ibáñez and published by Medical Encyclopedia, Incorporated, of New York, which is also the publisher of the other journals and volumes mentioned. This new series is designed to present more complete and comprehensive monographs on either individual antibiotics or general topics. Two of these monographs have already appeared. The first one, *Erythromycin*, is by Dr. Wallace E. Herrell, a recognized authority on antibiotics who, with his former colleagues at the Mayo Clinic, carried out some of the early studies on the clinical uses of penicillin and subsequently contributed to the understanding of each of the successive antibiotics as they appeared. It will be re-

called that Dr. Herrell, in 1945, presented one of the first comprehensive and practical books in this field, *Penicillin and Other Antibiotic Agents.* The monograph on *Erythromycin* gives, in 56 pages, a concise summary of the properties, pharmacology and practical applications of this agent.

The second monograph, recently released, is *Assay Methods of Antibiotics: A laboratory manual.* This one is by Dr. Donald C. Grove and Dr. William A. Randall, both of the Division of Antibiotics of the Food and Drug Administration, who are themselves responsible for many of the developments as well as the practical applications of these assay methods and are the authorities best qualified to cover this subject. This volume of 238 pages should serve as the source book for all laboratory workers who are confronted with the problem of assaying antibiotics.

Tetracycline is the title of Antibiotic Monograph Number 3 and is now ready for release; it is by Dr. Harry F. Dowling, professor of medicine and head of the Department of Medicine at the University of Illinois. Dr. Dowling is the author of the popular volume, *The Acute Bacterial Diseases: Their diagnosis and treatment.* He and his associates have made numerous valuable contributions to the clinical literature on antimicrobial therapy.

Monograph Number 4, entitled *Antibiotics in Nutrition,* which appeared early in October, is by Dr. Thomas H. Jukes, who, with his colleagues at the Lederle Laboratories and the Research Division of the American Cyanamid Company, pioneered the development of antibiotics as feed supplements to serve as growth-enhancing agents in animals raised for market. This volume presents a comprehensive review of the effects of antibiotics on the nutrition of animals and man and of the possible mechanisms by which this effect is accomplished. It should be of great interest to all those interested in nutrition, antibiotics and general biology, as well as in agriculture. Other important monographs by equally competent authorities on other topics of interest to practitioners and laboratory workers as well as to those in agriculture are planned.

Drs. Welch and Martí-Ibáñez are to be congratulated on their tireless efforts to present to the medical, pharmaceutical and scientific communities these very important and timely publications in an important field that now involves both human and veterinary medicine, as well as agriculture, general biology and organic, industrial and biologic chemistry.

HOMICIDE RATES FALL

THE belief is current that crimes of violence have materially increased during the tempestuous half century through which the world has most recently struggled. Rapid communication and improved as well as more dramatic methods of broadcasting the news have given strength to this belief, as sex crimes and those committed by adolescents, singly or in groups, have been featured.

When allowance is made for the rhythm of nature's processes, however, including the cyclic quality of patterns of behavior, it is found that criminality in the civilized countries of the earth is probably no more prevalent than it has been for a long time, and statistical evidence exists of an actual improvement over a period of years. There is no comparison, for instance, between the lawlessness that prevailed in much of Europe only two or three centuries ago and the relatively settled state of today; better policing has undoubtedly been a factor in this improvement but so also have been education and — perhaps most important of all — a higher standard of living.

Even in this supposedly turbulent country and despite recent reported increases in major crimes and juvenile delinquency, the homicide rate has fallen to a record low level. The Metropolitan Life Insurance Company's industrial policyholders, with an experience paralleling that of the country as a whole, have supplied the index, which shows a homicide death rate of 1.9 per 100,000 in 1954 compared with 5.8 in 1934. The downward trend has been marred by only two interruptions, occurring immediately after World War II and the Korean conflict.

Further analysis shows that the reduction has been most marked among white male policyholders, amounting to as much as 70 per cent, with a 50 per cent drop among white females and one of about 55 per cent among nonwhite policyholders. Homicide is still a major cause of death among nonwhite males, who averaged 21.7 per 100,000 in 1952-1954, or over eleven times the white male experience.

New England, despite a few untoward incidents, remains the safest place in which to live, in this respect, with the sunny South the most dangerous. Firearms represent the most commonly employed instrument of destruction, especially in agricultural areas. More than 7500 persons are still the victims of homicide in the United States each year according to *Metropolitan Information Service*; the rate among the white population being twice that in Canada and Australia, three times that in Scotland, and about six times that in England, Ireland and Wales.

Within the last twenty years a new method of applying electricity to medical purposes has been tried, and promises to become of greater practical utility than any other. This is the method of employing a wire, heated by galvanism to a red or white heat, instead of the knife, for some operations, and always instead of the old means of applying the actual cautery.

Boston M. & S. J., *Nov. 22, 1855*

MASSACHUSETTS MEDICAL SOCIETY

NOTICE TO FELLOWS

Copies of the *Circular of Advance Information for Councilors* for the February Council meeting will be available to any fellow who makes written request before December 2 to the Secretary of the Society, 22 Fenway, Boston 15.

ROBERT W. BUCK, M.D.
Secretary

COMMITTEE ON MATERNAL WELFARE

MITRAL REGURGITATION

A twenty-eight-year-old gravida IV, para III, with no history of rheumatic fever noticed increasing shortness of breath in the third month of pregnancy. In previous pregnancies, which resulted in delivery by cesarean section, there had been no evidence of heart trouble. The symptoms progressed, and orthopnea and hemoptysis developed, requiring hospital admission.

Physical examination and x-ray and electrocardiographic findings were characteristic of rheumatic heart disease, with preponderant mitral stenosis, for which appropriate and effective treatment was given. One week after admission valvuloplasty was attempted. When inserting his finger into the heart, the surgeon found only slight stenosis and mainly mitral insufficiency. A valvulotome was used to cut what stenosis did exist, but the surgeon thought that he had increased regurgitation by this. Biopsy of the left atrial appendage showed Aschoff bodies in the endocardium.

After operation the patient was hypotensive, with low serum sodium and high potassium levels. The liver was enlarged, but for some days she seemed to improve until eleven days postoperatively, when the apical systolic murmur seemed more prominent and x-ray study showed a considerable increase in heart enlargement. Another film showed a twin pregnancy. She was afebrile, but the pulse rate gradually increased to 110 to 120. It was decided that the pregnancy should be interrupted since it was believed that the heart could not stand the progressive burden of a twin pregnancy. On the eighteenth postoperative day she was transferred to a maternity hospital, where, in the nineteenth week of pregnancy, a miniature classic cesarean section and sterilization were done under epidural anesthesia. Cortisone was started shortly after operation because of the suspicion of active rheumatic fever. The patient stood the operative procedure well, but twenty-four hours later hyponatremia and a fall in carbon dioxide combining power developed. She was treated appropriately for this and gained in strength for about a week. She then suddenly became weak, short of breath and anorectic. The carbon dioxide combining power again fell, and she was again treated with sodium bicarbonate intravenously. Cortisone was withdrawn. Within eight hours the temperature rose, pleural friction rubs appeared bilaterally, and the pulse rate began to climb. Salicylates were started. Since interruption of pregnancy the heart rhythm had been atrial flutter, with varying degrees of atrioventricular block, relatively uninfluenced by digitalis. Now, when the pulse passed 150, an additional dose of digitoxin was given. It had little or no effect. On the thirteenth day after operation and the thirty-fifth day after valvuloplasty ventricular fibrillation suddenly developed, and she died.

Post-mortem examination did not confirm the clinical suspicion of active rheumatic fever and gave no anatomic explanation of the electrolyte imbalance, which, however, has been previously described in postvalvuloplasty patients. The valvulotomy incision, which was found in the anterior leaflet of the mitral valve, had extended into the anterior papillary muscle. The damage to this muscle was such that the effective range of motion of the leaflet was limited.

This case was classified as a preventable death due in the first instance to an error in diagnosis and in the second to errors in management resulting from the faulty diagnosis. A misdiagnosis of mitral stenosis, when actually the main lesion is mitral regurgitation, is an error that occurs even in the most experienced hands. On the other hand, the necessity or advisability of operation under the conditions that existed in this case would certainly not be universally admitted. It has been clearly demonstrated for many years that the great majority of patients with severe rheumatic heart disease can go through pregnancy safely and successfully with proper hospitalization and management. The results of such management are so good that cardiac disease is less and less frequently an indication for the termination of pregnancy.

The surgical operation did not diminish the burden on the patient's heart and did not improve her chances of going through pregnancy. Once operation had been performed and the subsequent downhill course followed, the situation was progressively difficult. In the opinion of the Committee, it is debatable whether the subsequent interruption of pregnancy was justified, but it should be emphasized that this opinion was reached after the fact.

JOHN FIGGIS JEWETT, M.D.
Chairman

NOTICES

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

There will be an informal reunion of the Boston University School of Medicine Alumni Association at the Sherry-Biltmore Hotel, Boston, Tuesday, November 29.

The social hour will be from 6 p.m. to 7 p.m. The dinner will begin at 7. Tickets will be held at the door, but should be ordered in advance. Invitations include family or friends.

ALPHA OMEGA ALPHA

A meeting of the Boston University School of Medicine Chapter of Alpha Omega Alpha will be held in the Auditorium, 80 East Concord Street, on Monday, November 28, at 5 p.m.

Dr. James A. Shannon will talk on "Poliomyelitis Vaccines."

All interested persons are invited.

NEW ENGLAND DIABETES ASSOCIATION

A meeting of the New England Diabetes Association will be held in the Joslin Auditorium, New England Deaconess Hospital, on Monday, November 28 at 8 p.m. Dr. Laurance W. Kinsell will give a talk entitled "Hypophysectomy in Juvenile Diabetics with Progressive Vascular Disease." Other speakers will discuss surgical and endocrine aspects of this problem.

AMERICAN COLLEGE OF CHEST PHYSICIANS AND OVERHOLT THORACIC CLINIC

A combined meeting of the New England States Chapter of the American College of Chest Physicians and the Overholt Thoracic Clinic will be held in the Joslin Auditorium of the New England Deaconess Hospital on Wednesday, November 23, at 4:00 p.m. Dr. William B. O'Brien will talk on "Collapse Therapy in the Drug Era."

AMERICAN PHYSICAL THERAPY ASSOCIATION MASSACHUSETTS CHAPTER

The Massachusetts chapter of the American Physical Therapy Association, in co-operation with the Polio Planning Committee of the Commonwealth, has made an extensive survey of physical therapists in the State, including a list of the personnel available for follow-up treatment of patients in the homes or on a part-time basis in hospitals and clinics. Further information may be obtained from the local chapter of the National Foundation for Infantile Paralysis, the local public-health office, or Nina G. Nichols, 296 Allston Street, Brookline 16, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 18–30. Consultation Clinics for Crippled Children in Massachusetts. Page 744, issue of October 27.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 21 and DECEMBER 5, 1955, and JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

NOVEMBER 22 and 29 and DECEMBER 6, 13 and 20. Boston City Hospital House Officers' Association. Page 793, issue of November 3.

NOVEMBER 23. American College of Chest Physicians and Overholt Thoracic Clinic. Notice above.

NOVEMBER 23, 1955–MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

NOVEMBER 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

NOVEMBER 28. Alpha Omega Alpha. Notice above.

NOVEMBER 28. New England Diabetes Association. Notice above.

NOVEMBER 29–DECEMBER 2. American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.

NOVEMBER 29. Boston University School of Medicine Alumni Association. Notice above.

NOVEMBER 30, 1955, and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 116, issue of July 21.

DECEMBER 1 and 2. New York-Bellevue Medical Center. Page 840, issue of November 10.

DECEMBER 5, 1955, and JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

DECEMBER 5–14, 1955, and JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

DECEMBER 7, 1955, and JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

DECEMBER 9 and 10. Association for Research in Nervous and Mental Disease. Page 745, issue of October 27.

DECEMBER 14, 1955, and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

DECEMBER 15. Arthritis Study Unit. Page 668, issue of October 13.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 24

THURSDAY, NOVEMBER 24
Holiday

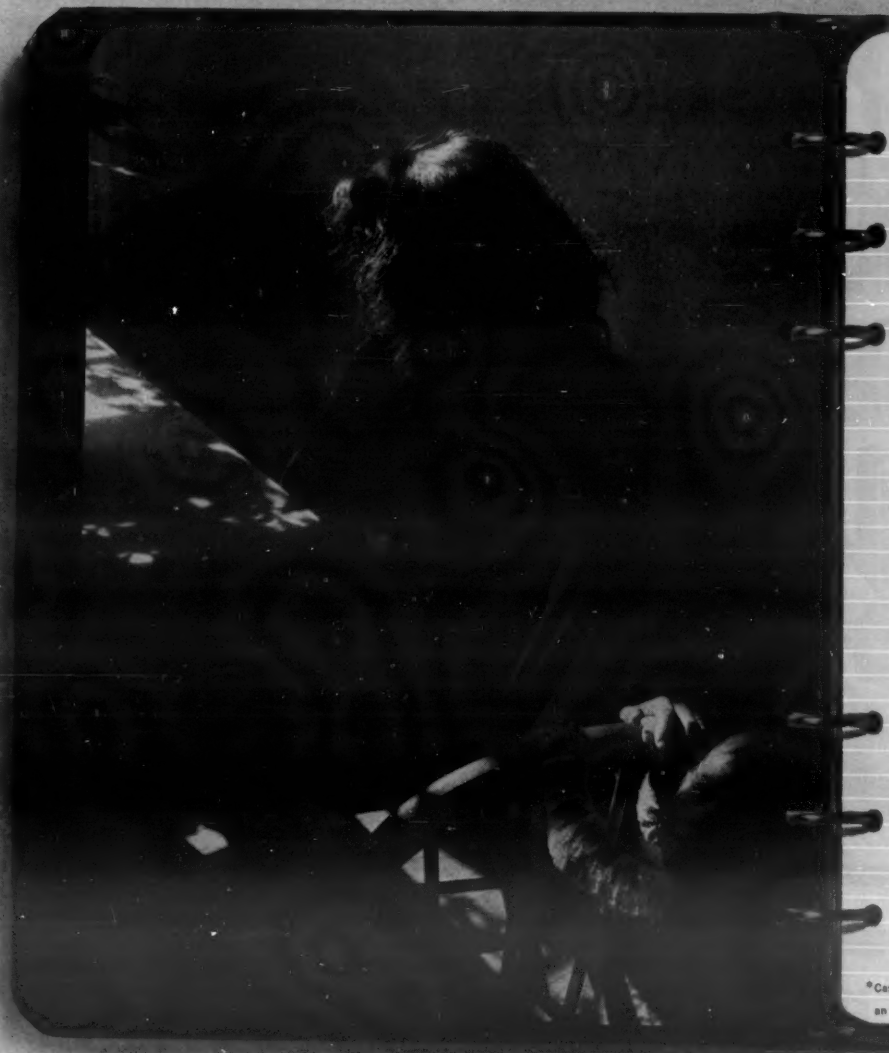
FRIDAY, NOVEMBER 25
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*7:30–9:30 p.m. Postgraduate Medical Institute. Dermatology. Drs. Appel and Catinella. Holyoke Soldiers' Home, Holyoke.

SATURDAY, NOVEMBER 26
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 28
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 am. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Medical-Pathological Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00 p.m. Alpha Omega Alpha. Auditorium, Boston University School of Medicine, 80 East Concord Street.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Controlled Respiration — Static Lung Volumes — Diffusion — Distribution — Ventilation. Dr. Crehan. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward H. MacMahon. Stearns Auditorium, New England Center Hospital.
*8:00 p.m. New England Diabetes Association. Hypophysectomy in Juvenile Diabetics with Progressive Vascular Disease. Dr. Laurence W. Kinsell. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, NOVEMBER 29
American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room. Carney Hospital, Dorchester.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xli)



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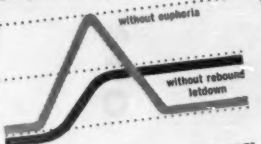

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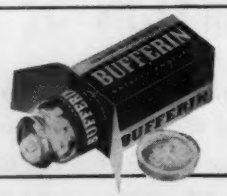

References: 1. Fremont-Smith, P.: J.A.M.A. 158:386, 1955. 2. J.A.M.A. 141:124, 1949. 3. M. Times 81:41, 1953.

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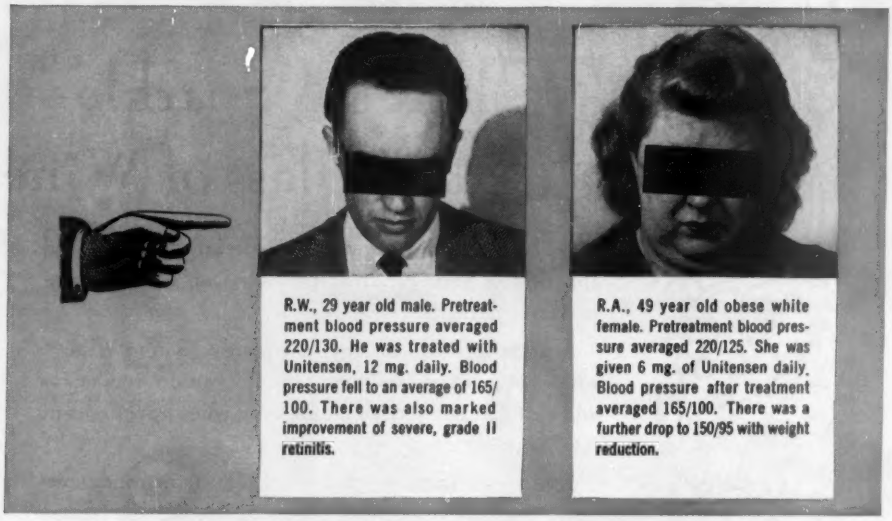

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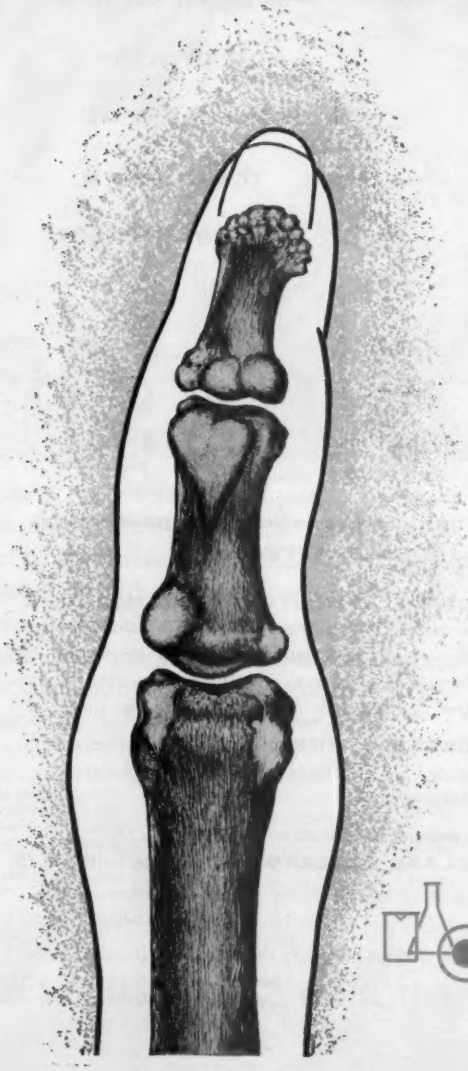

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1. Talbott, J. H.: Postgrad. Med. 5:386, May, 1949.

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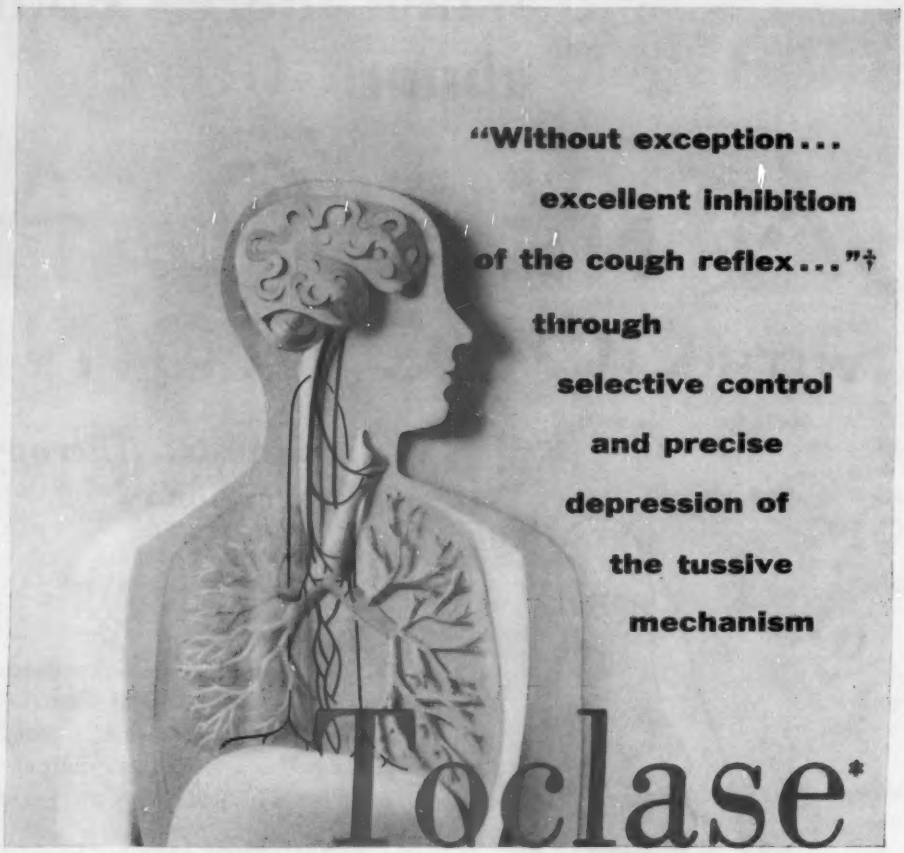

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Non-narcotic, non-constipating, non-sedating, non-nauseating, but HIGHLY SELECTIVE and HIGHLY EFFECTIVE

TOCLASE EXPECTORANT COMPOUND Reduces the frequency and intensity of unnecessary cough . . . moderates, but does not abolish purposeful, productive cough. Sugar free. Pleasant-tasting, cherry-flavored, amber color syrup. Bottles of one pint.

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for convenience at work or recreation
TOCLASE TABLETS 25 mg. tablets, bottles of 25.

†Parish, F. A.: M. Times *83*:870 (Sept.) 1955.

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Salcort performance stimulates a dependable response in arthritic conditions; early functional improvement and a sense of well being are significant. Smaller doses of salicylates and cortisone combined produce a therapeutic response equivalent to that of large doses of cortisone . . . side reactions are eliminated and continuous therapy is permitted. Salcort presents no withdrawal problems.

Each tablet contains:

Cortisone Acetate	2.5 mg.
Sodium Salicylate	0.3 Gm.
Aluminum Hydroxide Gel, dried	0.12 Gm.
Calcium Ascorbate (equivalent to 50 mg. Ascorbic Acid)	60 mg.
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PHYSICIANS' Office FURNITURE. All standard lines, new. Used equipment from time to time. Convenient terms. Visit our showroom close by Veterans Hospital. Ample parking. T. J. NOONAN Co., 408 South Huntington Avenue, Jamaica Plain (Boston 30), Mass. Phone JAmaica 2-8700 for literature. Medical, hospital, laboratory, sickroom supplies. B260-20-tf

AVAILABLE IMMEDIATELY — 1180 Beacon Street, Brookline, Mass. 3 rooms. Waiting room shared with one physician. 24-hour switchboard available. Suitable for internist, surgeon or dentist. Please call, ASpinwall 7-8332. B57-12-tf

OFFICE FOR RENT in professional building on Marlborough Street. 3 and 5 rooms. Elevator and janitor service. Reasonable rent. Further information, FAirview 3-3480. B33-7-tf

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FURNISHED AND/OR UNFURNISHED medical offices or suites, full time or part time. Telephone and secretarial services can be shared. Electric elevator. 110 and 220 AC current; entire floor available which can be remodeled to suit. Parking for doctors and patients. 350 Beacon Street, near Gloucester Street, river side. Building can be seen any time. Please telephone KEnmore 6-1364. B75-19-tf

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Olga C. Leary, M.D.
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Dependable and Rapid Laboratory Service. All Branches
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FOR SALE OR RENT — Ten-room house at Doctor's Row, 167 Maple Street. Occupied now as home and office. Moving to Florida. Will turn over well-established practice to suitable physician. Property can accommodate four doctors. Parking facilities good. This is a sound investment. Write or call James G. Makol, M.D., 167 Maple Street, Springfield 5, Massachusetts. Telephone RE 6-5175 or 6-0408. B70-18-4t

FOR SALE — X-ray. 100 MA combination fluoroscopic and radiographic tilt table with Bucky diaphragm. Complete darkroom accessories. Price reasonable. Call ALgonquin 4-5611. B71-18-3t

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STEROID & CLINICAL CHEMISTRY
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PEDIATRICIAN, certified, married, age 33, desires location or association, available Spring, 1956. Address A50, *New Eng. J. Med.* 18-4t

PHYSICIAN, licensed Massachusetts, extensive postgraduate training, desires part-time association with Internist or Pediatrician in Newton, Watertown area. Address A58, *New Eng. J. Med.* 19-2t

BOARD QUALIFIED INTERNIST, 34, with topnotch university training and excellent references, seeks permanent association with internist or medical group in Northeast. Address A57, *New Eng. J. Med.* 19-2t

COMPLETE PHYSIOTHERAPY SERVICE
JOHN A. BALENO, R.P.T.
Registered Physiotherapist
Patients accepted for treatment on doctor's prescriptions only.
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OFFICE FURNITURE—New—Used—Refinished. Bought and sold. Desk Clearing House, 115 Broad Street, Boston. HU 2-1318. B72-22-tf

FOR SALE — Large general practice, home, complete equipment and offices. Over $100 derived monthly from property. No charge for practice itself. New Hampshire town. Leaving to specialize. Address A246, *New Eng. J. Med.* 22-tf

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LABORATORY TECHNICIANS, registered M.T. (ASCP) preferred, male or female, for growing laboratory service in a 200-bed New England hospital. New, completely equipped laboratory. Salary open according to ability and experience. Address A28, *New Eng. J. Med.* 9-tf

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WANTED — Young physician interested to specialize in Allergy. Salary to start. Percentage with partnership to follow. Massachusetts license required. Give qualifications in first letter. Address A59, *New Eng. J. Med.* 20-2t

(Additional advertisements on page xxxviii)

1950 Cortone® | 1952 Hydrocortone®

1954 'Alflorone' | 1955 'Hydeltra'

DELTRA® tablets

(Prednisone, Merck) 5 mg. - 2.5 mg. - 1 mg. (scored)

the delta-1 analogue of cortisone

Indications:

Rheumatoid arthritis

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Conditioned Response, Psychotherapy, Antabuse, Adrenal Cortex and other drug therapies, Semi-Hospitalization for Rehabilitation of Male and Female Alcoholics.

Treatment of Acute Intoxication and Alcoholic Psychoses Included

State Outpatient Clinic and Social Service Department for Male and Female Patients

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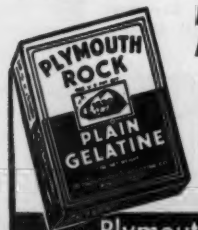

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Calories — 27 per envelope
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SEND FOR SAMPLES!

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Foot-so-Port Shoe Construction and its Relation to Weight Distribution

- Insole extension and wedge at inner corner of heel where support is most needed.
- Special Supreme rubber heels are longer than most anatomic heels and maintain the appearance of normal shoes.
- The patented arch support construction is guaranteed not to break down.
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- Foot-so-Port lasts were designed and the shoe construction engineered with orthopedic advice.
- **NOW AVAILABLE! Men's conductive shoes. N.B.F.U. specifications. For surgeons and operating room personnel.**
- By a special process, using plastic positive casts of feet, we make more custom shoes for polio, club feet and all types of abnormal feet than any other manufacturer.

Write for details or contact your local **FOOT-SO-PORT** *Shoe Agency. Refer to your Classified Directory*

Foot-so-Port Shoe Company, Oconomowoc, Wis.

Supplied: Bottles of 12 fluid oz.
Literature available.
1. Albert, A., and Albert, M.: Texas State J. Med. 50:814 (Dec.) 1954.
2. Sherber, D.A., and Levites, M.M.: J.A.M.A. 152:688 (June 20) 1953.

Reduces elevated blood cholesterol levels.[1,2]

Improves hypercholesteremic patients with cardiovascular disease and angina and those with postoperative biliary dyskinesia, both subjectively and symptomatically.[1]

monichol*

Polysorbate 80, Choline, Inositol—the new physio-chemical complex)

normalizes cholesterol metabolism

IVES-CAMERON COMPANY

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12 APPROVED ROTATING INTERNSHIPS available July 1956 to July 1957. Excellent teaching program. Affiliation with N.Y.U.-Bellevue Regional Teaching Plan. New 291-bed hospital in fine suburban community near N. Y. City. $125 per month plus full maintenance. Limited housing for married interns. Apply Director, Overlook Hospital, Summit, N. J. B74-19-5t

INTERNIST, BOARD QUALIFIED, married, 34, with 4 years' military service, now practicing in New England, desires relocation. Has been university-trained, with three years' residency and special interest in rheumatic diseases. Address A54, *New Eng. J. Med.* 19-4t

BAY STATE ROAD — Riverview office and examining room, share waiting room and laboratory, etc. KEnmore 6-0051. B60-20-1t

BRAND NEW Jones basal metabolism to be sold at a very reasonable price. Also a used infrared lamp. BEacon 2-4426. B76-20-1t

HOSPITAL DISCONTINUES SURGERY AND MATERNITY — For sale at a tremendous savings, a large assortment of practically new surgical instruments and supplies, 2 Major Operating Room tables with lights, Mayo table, anesthesia machine, instrument cabinet, T & A chair, scrub sinks and Septisol foot pedal dispensers, also Hotpoint incubator, bassinets and many other valuable hospital needs. Contact Copley Hospital, 224 Commonwealth Avenue, Boston or call COpley 7-5089. B235-19-3t

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POSITION OPEN at Boston Long Island Hospital. Assistant resident physician, $94 per week plus maintenance. Vacation and sick-leave benefits. Write Superintendent, Long Island Hospital, Boston 69, Mass. B68-17-4t

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WANTED — Nurse-secretary or medical secretary to work for prominent surgeon in Back Bay area. For further information, call KEnmore 6-3131. B78-20-tf

WANTED — Second-hand human skeleton for school. Quote price. Address A60, *New Eng. J. Med.* 20-2t

(Additional advertisements on page xxxvi)

more hemoglobin in less time

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a unique <u>new</u> compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
- iron your patients can tolerate
- no leg cramps with this iron-calcium

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EIGHT MILES FROM BOSTON

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring psychiatric, medical, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

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FRAMINGHAM, MASS.

A sanitarium specially adapted for nervous and convalescent patients who need rest and upbuilding in normal surroundings.
No committed mental cases.

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JAMAICA PLAIN, BOSTON, MASS.

A small, attractively located sanitarium for nervous, mild mental or chronic illnesses.

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LOCATED IN THE HILLS OF ESSEX COUNTY
30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; electric shock treatments, subcoma and deep coma insulin therapy when indicated; sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. SCHLOMER, M.D.
Medical Director

Wiswall Sanatorium

203 GROVE ST., WELLESLEY, MASS.

For the care of mild mental and nervous patients in country surroundings. Small grouping allows a homelike atmosphere and personal contact.

E. H. WISWALL, M.D., *Superintendent*
HALE POWERS, M.D., *Medical Director*
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STORROW HOUSE

(Former Storrow Estate at Lincoln, Mass.)
STAFFED AND OPERATED BY THE
MASSACHUSETTS GENERAL HOSPITAL

For nonpsychiatric ambulatory and semi-ambulatory patients needing rest or convalescent facilities.

CHARGES: $7.00 to $10.00 per day

Transportation for visits to physician's office provided. For information, call CLearwater 9-8343 or Massachusetts General Hospital Admitting Office LA 3-8200.

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Incorporated

WESTWOOD, MASSACHUSETTS

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A modern sanitarium for the treatment and care of mental and nervous disorders by a specialized staff experienced in psychotherapy, electroshock therapy and its modifications (electrocoma with or without electroshock) and other psychiatric treatments. Latest techniques used in the treatment of alcoholism and drug addiction. Excellent facilities for the care of senile and aged patients.

Homelike atmosphere in quiet country surroundings near Boston. Tennis court and occupational-therapy building on the grounds.

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BROOKLINE 46, MASS.

S. D. COHEN, R.N., *Supt.*
Convalescents — Invalid-Elderly
Accepted by Blue Cross - Blue Shield
Prolonged Illness Program

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Devoted to the scientific understanding and education of children of retarded development. Five homelike and attractive buildings surrounded by 85 acres of campus and gardens.

FRANKLIN H. PERKINS, M.D.

Serpasil®
(reserpine CIBA)

Elixir

Sedation without hypnosis

MEDICAL HORIZONS TV Monday P.M.

(Concluded from page 886)

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Physiologic Changes during Infection. Dr. Edward Kass. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, NOVEMBER 30

American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic, Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Bertram Selverstone, John F. Sullivan and Justin Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

THE SHOULDER

A two day course sponsored by the New York and Brooklyn Regional Committee on Trauma

to be held on

Friday, December 9th and Saturday, December 10th, 1955 at the Einhorn Auditorium, Lenox Hill Hospital, New York City

Cost of admission: Regular physicians..... $25.00
Hospital residents and internes..... $10.00

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DR. JESSE MAHONEY, Secretary
477 First Avenue
New York 16, New York

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Especially indicated for Old People and Children

Highly compatible vehicle

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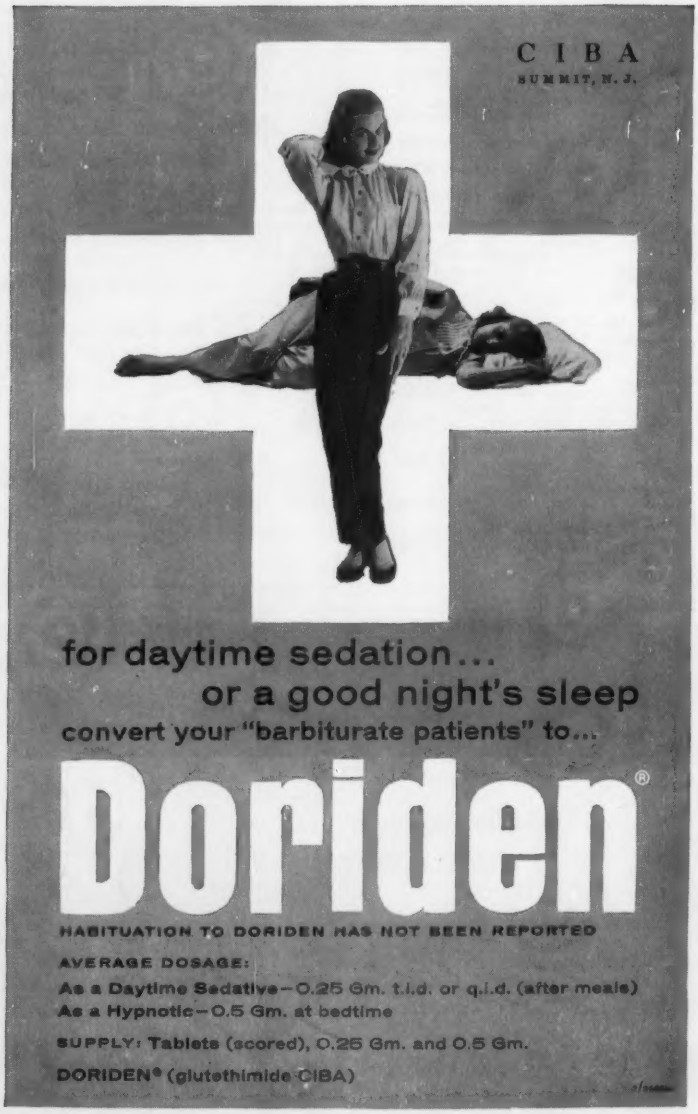
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AVERAGE DOSAGE:
As a Daytime Sedative—0.25 Gm. t.i.d. or q.i.d. (after meals)
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